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MAY 1946

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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CONTENTS

APRIL 1946. NUMBER 4

Results in the Treatment of Subacute Bacterial Endocarditis. Louis Levy II, M.D., and Ned McKrill, M.D., New Orleans.

Studies on Hypertension: VI. Effect of Lowering the Blood Pressures of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearances. Raymond Gregory, M.D.; William C. Levin, M.D.; Griff T. Ross, M.D., and Alene Bennett, B.A., Galveston, Texas.

A Roentgen Ray and Clinical Study of Primary Tuberculosis: Vollmer Patch Test Made on Four Hundred and Sixty Patients; Positive Reactions Secured in One Hundred and Fifteen. Alfred D. Biggs, M.D., with the Technical Assistance of Miss Irene Stolp, R.N., Chicago.

Electrocardiogram in Toxemias of Pregnancy. L. Wallace, M.D., Los Angeles, and L. N. Katz, M.D.; R. Langendorf, M.D., and H. Buxbaum, M.D., Chicago.

Prothrombin Level of Peripheral Blood and Sternal Marrow. Norman Rosenthal, M.D.; Sidney P. Zimmerman, M.D., and Shepard Shapiro, M.D., New York.

Progress in Internal Medicine:

Syphilis: A Review of the Recent Literature (Concluded). Charles F. Mohr, M.D.; Virgil Scott, M.D.; Richard D. Hahn, M.D., and Joseph Earle Moore, M.D., Baltimore.

Correspondence:

Arachnodactyly (Spider Fingers). E. Rosen, M.D., Newark, N. J.

Book Reviews.

ARCHIVES of INTERNAL MEDICINE

VOLUME 77 MAY 1946 NUMBER 5

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EFFECTS OF PLASMA AND FLUID ON PULMONARY COMPLICATIONS IN BURNED PATIENTS

Study of the Effects in the Victims of the Cocoanut Grove Fire

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CHARLES S. DAVIDSON, M.D.
AND
STANLEY M. LEVENSON, M.D.
BOSTON

THE victims of the Cocoanut Grove disaster, which occurred in Boston on the night of Nov. 28, 1943, offered a rather unusual opportunity for the study of the types of injury to the respiratory tract which may be expected when persons are exposed to smoke and flame resulting from rapid and extensive combustion in a relatively confined space. Since air conditioning has become commonplace and is increasing in popularity, the circumstances which gave rise to the Cocoanut Grove disaster might easily be duplicated in civilian life in situations in which combustible materials or mixtures of gases start to burn and cause an early disruption of the ventilating systems. Similar situations may arise when fires are caused by inflammable liquids or when explosives are set off or when fires gain headway in the holds of ships—and probably under many other circumstances. Few reports on the combination of extensive surface burns and severe injuries of the respiratory tract similar to those of the persons hurt in the Cocoanut Grove fire are available in the literature.[1]

The work described in this paper was done, in part, under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), and the Burn Assignment to the Surgical Services, Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

1. (*a*) Nichols, B. H.: The Clinical Effects of the Inhalation of Nitrogen Dioxide, Am. J. Roentgenol. **23**:516-520, 1930. (*b*) Beckey, K., and Schmitz, E.: Klinische und chemische Beiträge zur Pathologie der Verbrennung., Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:416-432, 1918-1919. (*c*) Fischer, B., and Goldschmid, E.: Ueber Veränderungen der Luftwege bei Kampfgasvergiftung und bei der Verbrennung, Frankfurt. Ztschr. f. Path. **23**:11-33, 1920.

One of the important features of the management at the Boston City Hospital of the patients who were injured in the Cocoanut Grove fire was the rather large volumes of plasma and other fluids that were used in the treatment of many of the patients. That, too, was considered to be rather unusual at the time, although it has since become a not infrequent practice in the treatment of patients with extensive surface burns. We are aware of no other reports of the use of similar amounts of plasma and other parenteral fluids in persons with such extensive pulmonary lesions. An analysis of the effects of this therapy on the complications in the respiratory tract in the present cases may, therefore, be of interest. Details of the clinical features of these complications, as observed at the Boston City Hospital, are recorded elsewhere,[2] and a description of the observations made concerning the victims of this fire who were treated at the Massachusetts General Hospital is included in the comprehensive report from that hospital.[3] The surgical and biochemical studies on the patients treated at the Boston City Hospital are considered in separate reports by Dr. C. C. Lund and Dr. F. H. L. Taylor and their associates.[4]

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2. (*a*) Finland, M.; Davidson, C. S., and Levenson, S. M.: Clinical and Therapeutic Aspects of the Conflagration Injuries to the Respiratory Tract Sustained by Victims of the Cocoanut Grove Disaster, to be published. (*b*) Finland, M.; Ritvo, M.; Davidson, C. M., and Levenson, S. M.: Roentgenologic Findings in the Lungs of Victims of the Cocoanut Grove Disaster, Am. J. Roentgenol. **55**: 1-15, 1946.

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For convenience the severity of the injuries to the respiratory tract were graded according to the symptoms and physical findings roughly as follows:

Grade	Clinical Manifestations
0.	No signs or symptoms referable to the respiratory tract.
1.	Signs and symptoms, including mild laryngitis, limited to the upper respiratory passages.
2.	Evidence of involvement of the trachea and bronchi, or abnormal signs in the lungs other than those of frank consolidation.
3.	Dyspnea, cyanosis, wheezing or transient stridor, or frank signs of consolidation.
4.	Evidence of extensive pulmonary involvement or of obstruction to the airways necessitating tracheotomy or resulting in severe asphyxia.

In general, the extent of the abnormalities found in the lungs by roentgenologic examination reflected the severity of the clinical findings fairly closely, but in an appreciable number of cases the clinical symptoms were much more severe than might have been expected from the lesions visible in the roentgenograms.[2b] There was also some direct correlation in most cases between the extent of the surface burns and the severity of the injuries to the respiratory tract. Both here and at the Massachusetts General Hospital, however, there were cases of severe and even fatal respiratory lesions in which surface burns were either absent or minimal. Likewise, at both hospitals there were occasional cases of extensive and even fatal surface burns in which there was little or no evidence of involvement of the respiratory tract. These discrepancies could usually be explained by the peculiar cimcumstances in the individual cases.[2a]

As far as could be determined, all the patients who manifested evidence of pathologic conditions in the respiratory tract at any time during their stay in the hospital had definite symptoms of such involvement during the first twenty-four hours. In some cases, to be sure, the symptoms increased in severity after that time. It seems reasonable to suppose, however, that the management of the early phase of the treatment, when shock was present or imminent in many of the cases, had a significant effect on the subsequent course and possibly influenced the severity of the pulmonary symptoms and even the final outcome in some of the cases.

There were considerable interest and concern among the workers here during the first few hours about the possible effects of the injection of large amounts of fluid, particularly plasma and isotonic solution of sodium chloride, on the pulmonary lesion. It is usually assumed from what has been written concerning the treatment of the effects of pulmonary irritants, particularly in gas warfare, that bloodletting is the proper procedure to use in the treatment of pulmonary edema

resulting from such irritants. That seemed reasonable in some ways, although the exact physiologic mechanism involved is not clear. With respect to many of the present patients, however, the possibility that pulmonary edema was present or might develop was clearly overshadowed by the presence of unmistakable evidence of shock. To such patients saline solution and plasma were given freely, and the fluids seemed to produce obvious improvement in most instances without any apparent adverse effect on the respiratory symptoms. This encouraged the use of such fluids also for patients with predominantly respiratory injury and with only minor surface burns when signs of imminent shock were observed. To a few of the patients, to be sure, it was felt at the time that excessive amounts of saline solution may have been given, particularly before an adequate supply of plasma became available, but this probably did not occur after the first few hours.

It was pointed out elsewhere [2a] that evidence of frank pulmonary edema was not made out clinically in the early hours in many cases, unless the scattered crepitant rales heard in many of the very sick patients in the dependent parts of the lungs, and in some instances in other parts of the lungs as well, were the manifestations of such edema. In some patients, who were obviously dying, the tracheal rales and frothy exudate in the mouth were considered to be terminal events, which yielded to no form of treatment that was offered. Measurements of venous pressure or of the oxygen saturation of the blood unfortunately were not made. However, considerable degrees of engorgement of the cervical veins, suggesting increased venous pressure, were not seen except during the period of acute anoxia, when the patients were noticeably excited and dyspneic as a result of obvious obstruction to respiration.

Because of the great interest in this phase of the early management of the cases, the total amounts of the various forms of fluid actually given and recorded in each case are listed in tables 1 and 2 together with the extent of the patient's surface burn and the grade of the severity of the respiratory symptoms. These tables include data on all of the patients admitted to the wards of the Boston City Hospital from the Cocoanut Grove fire except on those who had slight or no surface burns or respiratory symptoms and on 2 patients who died before fluids could be given.

The data concerning the fluid balance were also of prime interest in the first day because of the necessity of there being a good output of urine if sulfonamide therapy were to be used—and it seemed desirable to institute such therapy as early as possible. This aspect as well as other phases of the emergency treatment, such as the use of oxygen,

TABLE 1.—*Fluid Balance During First Twenty-Four Hours and Other Relevant Data in Survivors*

Data for 28 patients with few or no burns and with little involvement of the respiratory tract are omitted.

Case No.	Sex	Age	Burn, per Cent of Body Surface	Grade of Respiratory Involvement (Clinical)	Fluid Intake, Liters				Urine Output	Day of Discharge
					Parenteral					
					Plasma,* Units	0.85% NaCl	5 or 10% Dextrose	Oral Fluids		
1	F	30	7	3	4	1.0	0	0.3	0.4	16
3	F	20	1	3	6	1.5	0	...†	...	15
4	F	33	6	2	4	0	1.5	0.2	0.7	96
5	M	21	6	1	3	1.5	0	1.3	0.9	25
6	M	44	6	1	2	1.5	0	1.2	0.8	39
8	M	22	4	3	10	4.5	0	2.3	1.5	23
9	M	26	5	2	8	1.5	0	2.3	1.3	20
10	F	22	3	2	3	3.0	0	...	0.3	15
11	M	39	16	3	10 (1)	0	1.5	1.4	1.5	35
12	F	22	1	2	4	0	0	0.3	1.0	24
13	M	24	2	2	3	1.5	0	0.5	0.3	11
14	F	30	4	2	2 (1)	1.5	0.5	0.9	0.5	24
15	F	30	20	1	4	0.5	0	...	...	197
16	F	20	2	3	3	2.5	0	...	0.7	15
17	F	30	30	2	7	3.0	0	1.0	0.5	200
18	M	26	3	0	1 (2)	1.5	1.5	1.5	0.5	36 hours‡
19	M	23	6	3	10	2.0	0	0.9	0.6	69
20	F	25	0	1	3	0	0	0.5	0.4	4
21	M	25	6	2	14	1.5	0	1.2	1.6	13
22	M	35	6	3	13 (2)	0	0	1.4	1.4	31
23	F	30	10	2	4	4.5	0	0.3	0.9	125
24	M	26	14	3	14	1.5	0	2.2	2.5	130
26	M	20	5	1	3	1.5	0	0.8	1.3	20
27	F	41	0	1	5	0	0	5.3	4.5	8
28	F	27	25	1	6	2.5	1.5	1.2	0.8	87
29	F	38	5	2	6	3.0	0	0.4	0.4	36 hours‡
30	M	30	4	2	7	1.5	0	1.6	1.2	18
31	M	33	3	1	4	1.4	0	0.6	0.6	14
34	M	35	2	1	2	1.5	0	...	...	11
35	M	25	5	2	16	1.0	0	4.2	2.4	25
36	M	34	3	1	2	1.5	0	3.8	1.1	13
37	M	25	6	3	9	1.5	1.5	...	1.1	17
38	M	22	55	2	17	1.5	1.5	2.0	1.6	365
39	M	33	8	1	6	1.5	0	0.3	0.4	28
41	M	22	1	2	0	0	0	0.8	...	11
43	M	25	5	1	0	1.0	0	1.3	0.3	10
47	F	23	0	3	8	0.8	0	0	0.2	18
49	F	28	25	3	12	4.5	0	...	1.9	120
50	F	22	2	2	6	0	0	0.1	...	14
51	F	17	28	2	5	0	0	0.2	...	155
52	F	23	2	3	6	3.0	0	...	...	17
53	M	28	1	3	7	0	3.0	0.8	2.1	11
54	F	28	10	1	4	0.5	0	0.2	0.2+	120
55	F	23	5	0	2	1.0	0	...	...	14
56	M	49	2	1	0	0	0	1.0	0.7	9
57	M	21	3	1	2	0	0	0.9	0.7	14
58	F	28	13	2	17	0.7	0	0.5	0.4	145
59	F	30	8	1	1	1.5	0	...	...	113
60	M	25	4	1	1	0	0	...	...	8
61	M	32	6	2	11	1.5	0	2.3	1.7	58
62	F	29	6	1	5	3.0	1.5	...	...	61
63	F	37	5	1	0	0.7	0	1.9	1.5	7
64	F	22	3	3	1	3.0	0	0.3	0.3	19
65	F	22	6	3	6	3.0	0	...	...	67
66	F	23	1	2	4	0	0	0.7	0.2	31
67	M	23	11	1	11	1.5	0	1.7	1.2	18
68	M	21	5	0	11	1.5	0	1.0	0.9	68
69	M	26	6	3	5	1.5	0	1.2	1.4	24
70	M	36	2	3	2	1.5	0	0.2	0.5	10
86	M	57	6	2	1	3.0	0	0.1	1.3	15 hours‡
89	M	25	2	0	1	1.5	0	...	...	12 hours‡
90T§	F	17	5	4	6	1.5	0	...	...	66
91T	M	50	6	4	7 (1)	5.0	0	0.3	1.4	20
92T	F	32	0	4	2	1.5	0	0.2	0.7	23

* Parentheses enclose additional number of units of albumin. One unit of albumin is equivalent to 100 cc. of a 25 per cent solution, or the osmotic equivalent of 2 units of plasma.

† Leaders indicate that data are not available.

‡ Tranferred to another hospital.

§ T = tracheotomies.

sedatives and stimulants, is considered elsewhere.[5] The effects of the plasma and other fluid intake in combating shock are considered elsewhere by Dr. Lund and Dr. Taylor and their associates.[4]

A total of 693 units of plasma, each consisting of 250 cc., and 17 units of albumin, each containing 25 Gm. in 100 cc. of water, were

TABLE 2.—*Fluid Balance During First Twenty-Four Hours and Other Relevant Data in Fatal Cases*

Data for 2 patients who died in less than three hours without receiving fluids or plasma are omitted.

Case No.	Sex	Age	Burn, per Cent of Body Surface	Grade of Respiratory Involvement (Clinical)	Fluid Intake, Liters: Parenteral: Plasma,* Units	Parenteral: 0.85% NaCl	Parenteral: 5 or 10% Dextrose	Oral Fluids	Urine Output	Death, Time after Fire
93T†	M	28	5	4	8 (1)	0	7.0	0	1.0	31 hours
94T	F	25	25	4	9	0	3.0	...‡	...	26 hours
95T	F	22	60	4	8	1.2	0	0.1	0.8	28 hours
96T	M	50	6	4	4	0	0	...	...	9 hours
97T	M	44	5	4	9	1.5	0	...	0.2	16 hours
98T	F	43	<1	4	4	1.5	1.0	...	...	78 hours
99T	F	25	20	4	6	1.5	0	...	...	6 hours
100T	M	30	13	4	18	1.5	1.0	...	...	24 hours
101T	F	22	14	4	10	0	4.5	...	...	34 hours
102T	F	22	65	4	10 (3)	3.5	0	1.4	0.8	30 hours
103T	F	31	4	4	8	0	1.5	...	0.8	15 hours
104T	F	19	¥	4	6	3.0	0	0.5	1.8	4 days
105T	F	27	15	4	4	3.0	0	...	...	17 hours
106T	F	23	35	4	11	0.5	0	4.5	0.8	50 hours
107T	F	45	12	4	7	4.5	0	1.0	0.6	7 days
108	M	29	65	3	2	3.0	0	...	...	6 hours
109	F	22	30	2, A0§	16	1.5	0	...	...	157 days
110	M	19	30	2, A4	10	0	0	3.3	0.5	28 days‖
111	M	41	60	3	17	0	2.5	...	0.4	24 hours
113	F	22	30	3	13 (3)	1.0	0	2.0	0.6	9 days
114	F	24	30	3	6	0	0	...	...	10 hours
115	F	33	65	3	10	1.5	0	...	1.1	29 hours
116	M	31	30	4	7	1.5	0	...	0.1	24 hours
117	M	42	40	2	3	0	0.5	...	...	4 hours
118	M	21	4	4	3	0	0	...	...	7 hours
119	M	25	45	4	7 (2)	1.5	1.0	0.7	0.8	5 days
120	F	29	65	4	20	0.5	2.5	1.5	0.8	79 hours
122	F	54	8	4	10	1.5	0	...	0.8	38 hours
123	F	23	0	4	9	1.5	1.0	...	0.4+	25 hours
124	M	31	10	4	12 (1)	2.0	0	0.4	1.3	43 hours
125	M	25	45	4	7	4.2	0	...	0.2	6 days
126	M	50	55	4	12	3.0	2.0	1.8	0.4	42 hours
127	F	35	60	1, A3	22	2.0	0	...	0.3	9 days
128	M	34	30	0	7 (1)	1.5	0	3.0	0.6	80 days
129	M	53	8	4	2	1.5	0	...	...	4 hours
130	M	26	45	3	4	0	0	...	...	12 hours
131	F	29	45	3, A4	11	3.0	1.5	0.8	0.2	13 days

* Parentheses enclose additional number of units of albumin. One unit of albumin is equivalent to 100 cc. of a 25 per cent solution, or the osmotic equivalent of 2 units of plasma.

† T = tracheotomies.

‡ Leaders indicate that data are not available.

§ A0, A3 and A4 indicate grade of involvement of the respiratory tract observed at autopsy.

‖ Patient spent last six days at another hospital.

given to 98 of the patients. If one considers each unit of albumin as the osmotic equivalent of 500 cc. of plasma, the average amount of plasma

5. Finland, M.; Davidson, C. S., and Levenson, S. M.: Chemotherapy and Control of Infection Among Victims of the Cocoanut Grove Disaster, Surg., Gynec. & Obst. **82**:151-173, 1946; footnote 2*a*.

and albumin used in these 98 patients was the equivalent of 7.4 units, or 1,850 cc. of plasma. In addition, a total of 149 liters of 0.85 per cent sodium chloride solution, some of which also contained 5 per cent of dextrose, was given intravenously to 77 of the patients. Only 3 liters of this total was given to patients, 3 in number, who received no plasma. Thus 74 patients received an average of 2 liters of saline solution intravenously in addition to plasma during the first twenty-four hours after the fire. Still more fluids of various kinds were taken orally by most of the patients, and a number of them received intravenous injections of 5 or 10 per cent solutions of dextrose in distilled water. It is not unlikely that still more of the various forms of fluids were given to others and even to some of the same patients and that records of the fact were not made or were lost.

TABLE 3.—*Summary of the Fluid Intake in the Cocoanut Grove Victims During the First Day: Arranged According to the Grade of Severity of the Respiratory Complication*

Grade of Respiratory Involvement	Number of Cases in Group	Plasma		Intravenous Sodium Chloride, 0.85% Solution		Other Fluids *	
		Number of Cases	Average Number of Units per Patient	Number of Cases	Average Amount, Liters	Number of Cases	Average Amount, Liters
0	24 (1)†	8 (1)	4.4 (9)	7 (1)	1.4 (1.5)	5 (1)	1.8 (3.5)
1	33 (1)	20 (1)	6.3 (22)	18 (1)	1.5 (2.0)	19	1.8
2	19 (3)	18 (3)	7.0 (9.7)	12 (1)	2.1 (1.5)	16 (2)	1.1 (1.9)
3	25 (7)	24 (7)	8.4 (10)	18 (4)	2.2 (2.1)	15 (3)	1.6 (2.3)
4	30 (27)	28 (25)	8.5 (8.8)	22 (19)	2.1 (2.1)	18 (16)	2.1 (2.3)
All groups	131 (39)	98 (37)	7.4 (9.5)	77 (26)	1.9 (2.0)	73 (22)	1.6 (2.3)

* Presumably almost all of the fluids given intravenously, which consisted mostly of 5 per cent or occasionally 10 per cent dextrose solution, are included here and all of the isotonic solution of sodium chloride given parenterally is included in the preceding columns. Satisfactory records of the fluids taken orally were kept only in a minority of the cases, and the amounts taken by the remaining patients are not included in this column. Many of the latter, however, were patients who were discharged to other hospitals or who died during the first day.

† The parentheses enclose the figures for the fatal cases alone.

A summary of the average amounts of fluids of all sorts, including plasma, that were given to the patients admitted from the fire, is presented in table 3. In this table the cases are arranged according to the severity of the respiratory involvement. It is seen that a smaller proportion of the patients without respiratory symptoms and of those with the milder grades of involvement received these fluids, particularly the saline solution. From this table, however, it is not clear which of the patients within each group received each of the various kinds of fluid. It is desirable to know whether those patients who received large volumes of plasma also received significant amounts of the other types of fluids or whether the latter were reserved for patients for whom plasma was not used or to whom it was given in only small amounts.

The data bearing on this point are shown in table 4. In this table the number of patients receiving various amounts of plasma are shown, and for each group of patients the number receiving saline solution and other fluids and the average amounts of such fluids are given. It is seen that the proportion of patients receiving both saline solution and other fluids actually increased with the amount of plasma used and that the average amount of fluids likewise was greater for the patients who received large amounts of plasma than for those who received none or small amounts, except for the patients who received more than 3 liters.

As might be expected, the amount of plasma given was, generally speaking, based on the rate and quality of the pulse, on the blood pressure and, later in the day, on the hemoglobin and hematocrit values.

TABLE 4.—*Correlation of the Amounts of Solution of Sodium Chloride and Other Fluids Given During the First Day with the Amounts of Plasma Administered During the Same Period*

Plasma		Isotonic Solution of Sodium Chloride		Other Fluids	
Number of Cases	Number of Units	Number of Cases	Average Volume,* Liters	Number of Cases	Average Volume,* Liters
33 (2)†	0	3	1.1	5	1.1
52 (11)	1 to 6	28 (6)	2.6 (2.3)	31 (3)	1.0 (0.7)
32 (18)	7 to 12	24 (13)	2.3 (2.1)	25 (13)	2.3 (2.9)
14 (8)	13 or more	12 (7)	1.3 (1.7)	12 (6)	1.9 (1.9)
131 (39)	7.4 (9.5)‡	77 (26)	1.9 (2.0)	73 (22)	1.6 (2.3)

* Averages exclude those who received none of the fluids in question.

† The parentheses enclose the figures for the fatal cases alone.

‡ Averages.

These in turn were related in a general way to the extent of surface burned. Since most of the patients with extensive surface burns also had severe involvement of the respiratory tract, it would appear that the amount of plasma given was also related to the severity of the respiratory lesions. This is brought out clearly in table 5, in which the number of patients receiving varying amounts of plasma is correlated with the percentage of the body surface burned, on the one hand, and with the severity of the respiratory symptoms, on the other.

It is seen from table 5 that, as the extent of the surface burn increased, fewer of the patients failed to receive plasma therapy and that the average amount given to the others increased with the extent of the surface involved. Likewise, two thirds of the patients without definite respiratory involvement and 39 per cent of those with minor symptoms (grade 1) received no plasma at all, whereas only 1 or 2

of each of the groups of patients with the more severe grades of respiratory damage failed to receive any. And here again, the average amounts of plasma given increased with the severity of the respiratory lesions.

NOTES ON ILLUSTRATIVE CASES

From the point of view of the individual patients, those without burns or with only minor surface burns who received large amounts of plasma are of special interest. A few such patients, who received more than 2 liters of plasma or their equivalent in albumin in addition to other parenteral or oral fluids, and who had burns involving only 6 per cent or less of their body surface, may be considered here. A brief note concerning the intake of fluid and the respiratory symptoms in

TABLE 5.—*Relation of the Amount of Plasma Administered During the First Twenty-Four Hours to: A, the Extent of the Body Surface Burned and B, the Degree of Respiratory Damage*

Units of Plasma *	A. Percentage of Body Surface Burned					B. Degree of Respiratory Damage					Total	
	0	1-4	5-9	10-29	30+	0	1	2	3	4	Cases	Per Cent
0	12 (1)†	17	3	1 (1)	0	16	13	1	1	2 (2)	33 (2)	25
1-4	2	17 (2)	10 (2)	4 (1)	3 (3)	5	11	8 (1)	6 (2)	6 (5)	36 (8)	27
5-8	2	7 (1)	9 (2)	4 (2)	5 (4)	1	5	5	7 (1)	9 (8)	27 (9)	21
9-12	1 (1)	1	7 (2)	5 (2)	7 (7)	2 (1)	1	2 (1)	7 (2)	9 (8)	21 (12)	15
13+	0	0	3	4 (2)	7 (6)	0	3 (1)	3 (1)	4 (2)	4 (4)	14 (8)	12
All cases	17 (2)	42 (3)	32 (6)	18 (8)	22 (20)	24 (1)	33 (1)	19 (3)	25 (7)	30 (27)	131(59)	100
No plasma: % of cases	71	40	9	5	0	67	39	5	4	7		25
Average ‡	5.4	4.0	6.8	9.2	11.1	4.4	6.3	7.0	8.4	8.5	7.4	

* Includes albumin; 25 Gm. of albumin are equivalent to 2 units of plasma.

† The parentheses enclose the numbers of fatal cases included.

‡ Average number of units of plasma per patient, excluding those who received none.

each of these cases will serve best to exemplify the effects of the large intake of plasma and of other fluid under these circumstances.

One of these patients (case 8) had burns involving only 4 per cent of the body surface and received during the first twenty-four hours a total of 10 units (2,500 cc.) of plasma in addition to 4.5 liters of isotonic solution of sodium chloride intravenously and about 2,300 cc. of fluids orally. During this same period his output of urine was about 1,500 cc. When this patient was first admitted to the ward there were second degree burns on his face and hands, his voice was very hoarse and he was coughing and felt chilly. Crepitant rales were heard at the bases of the lungs, and high pitched musical rales were heard in inspiration throughout both lungs. In the course of the first twenty-four hours his respiratory distress increased slightly, but the physical signs were essentially the same at the end of this period and also on the following morning. This patient later raised copious amounts of green purulent sputum from which type III

pneumococci were identified. In the past he had had severe colds about four times a year, and each one left him with a protracted cough productive of much sputum. As far as it could be ascertained, the large amounts of plasma and other fluids which this patient received did not have any unfavorable effect on the respiratory complication. Certainly no truly "wet lung" resulted from the large intake of fluid in this case.

The burns in case 21 involved an estimated 6 per cent of the patient's body surface and were limited to the face, ears, neck and hands. At the time of admission this patient was restless and uncomfortable from the pain of his burns; his blood pressure was 98 systolic and 55 diastolic, his pulse rate was 108 and his lungs were clear to auscultation and percussion. Within four hours he received 1,500 cc. of isotonic solution of sodium chloride and 7 units of plasma, after which his pulse rate was 126 and his blood pressure rose to 130 systolic and 85 diastolic, and remained at this level. By the end of the first twenty-four hours he had received 7 additional units of plasma and taken about 1,200 cc. of fluids by mouth, and his output of urine for the same period was about 1,600 cc. During this time he remained restless, in spite of sedatives, and his temperature rose to 103.4 F., but except for a slight cough and moderate hoarseness, he experienced no apparent respiratory distress. On the following morning the breath sounds were diminished at the base of the left lung but a roentgenogram taken at that time showed no evidence of pulmonary congestion or edema. The large volume of plasma plus the other fluids given to this patient certainly did not aggravate his respiratory symptoms.

Case 22 was another one with burns involving 6 per cent of the patient's body surface—in this instance including the face, hands, forearms and part of the thoracic wall. On admission this patient had a severe cough productive of black-stained mucoid sputum, and shortly thereafter musical and crepitant rales were heard at the bases of both lungs. Injections of plasma were started at 2 a. m., and he received a total of 3,250 cc., in addition to 50 Gm. of albumin (the equivalent of another liter of plasma), within the first twenty-four hours. There is no record of his having received any other fluids intravenously, although some may have been given, but the patient took 1,400 cc. of fluids by mouth and passed about 1,400 cc. of urine during this time. The blood pressure was 120 systolic and 80 diastolic before the first injection of plasma and remained at this level or slightly higher throughout the first two days. Late in the afternoon of the first day the patient began to have dyspnea and stertorous breathing, and this difficulty increased late that evening, but it improved rapidly after oxygen therapy was started. On the following day the patient had several periods of restlessness and dyspnea, and at these times he coughed frequently and raised moderate amounts of tenacious blood-streaked sputum. He also blew large amounts of similar but crusted material from his nose. Large numbers of pneumococci were found in the sputum. The patient subsequently began to show signs of frank consolidation, which proved to be associated with complete collapse of the left lower lobe. Although in this patient there was severe damage to the upper respiratory tract and bronchopulmonary damage, there is no reason to believe that these lesions were seriously influenced by the plasma and albumin or by the other fluids which he received.

In case 35 there were burns of an estimated 5 per cent of the patient's body surface and involving the face, ears, dorsa of both hands and the lower part of the forearms. At the time of the patient's admission to the ward no abnormal physical signs were made out in the lungs, and the throat was clear. Plasma therapy was started within twenty minutes of his arrival, and by the end of twenty-four hours he received a total of 16 units of plasma and a liter of saline solution intravenously and, in addition, took about 4,200 cc. of various fluids by mouth. His output of urine for this period was 2,400 cc. This patient's blood pressure was 160 systolic and 80 diastolic, and his pulse rate was 100 before the plasma was started. Except for a drop in systolic pressure to 140, there was no striking change during the first twenty-four hours; on the following day there was only a slight cough and tracheitis, and the lungs remained clear to physical examination. Some changes were noted, however, in the roentgenogram taken on the second day. No ill effects could be attributed in this case to the plasma given or to the initial large intake of fluid, at least as far as the pulmonary complication was concerned.

Case 91 is of interest because in this case a large amount of saline solution was used for a patient with a severe bronchopulmonary lesion. The patient was a large, obese man of 50 who had a history of severe hay fever and of a chronic cough productive of much thick mucus. He was just recovering from a severe cold and sore throat at the time of the fire. He had inhaled a large amount of smoke, but his burns were limited chiefly to the face and hands and involved about 6 per cent of the body surface. At midnight, when he first arrived in the ward, he was having repeated chills, was coughing violently and expectorating copious amounts of thick, black-stained sputum. His blood pressure at that time was 150 systolic and 70 diastolic, his pulse 112 and his respirations 28 per minute. Injections of saline solution and of human albumin were soon started, and by mid-afternoon he had received a total of 5 liters of isotonic solution of sodium chloride, 100 cc. of a 25 per cent solution of albumin (or the osmotic equivalent of 500 cc. of plasma) and 1,250 cc. of plasma. During this time he had steadily increasing restlessness, dyspnea and stridor and continued to raise thick masses of black sputum until finally his breathing became completely obstructed and an emergency tracheotomy was required. It was necessary to follow this procedure with frequent bronchoscopic suction because of recurrent obstruction of the air passages below the tube, and artificial respiration was resorted to several times before breathing was restored. There was evidence of considerable moisture throughout both lungs all of that day, but there was little change in the pulse and blood pressure except during the periods when he was struggling and restless because of the anoxia which resulted from intermittent obstruction to respiration. The suction gave considerable relief from the dyspnea each time. In this case, which ended in the patient's recovery, the possibility that the large volume of saline solution, when added to the plasma and albumin, contributed to the moisture in the lungs cannot be ruled out. The chief difficulty, however, obviously was due to the changes in the bronchi, and whatever pulmonary edema may have been present could be attributed mainly to anoxia from this cause.

One other case, number 123, may be mentioned. This patient was semicomatose on admission and had "noisy and labored respirations" at the time. She was

also very hoarse and had a "croupy cough." No surface burns were seen. She lived only twenty-five hours after being brought to the hospital. During this time she received 2,250 cc. of plasma, 1,500 cc. of isotonic solution of sodium chloride and 1,000 cc. of a 5 per cent solution of dextrose in distilled water by the intravenous route, and took a small but unknown quantity by mouth. She voided 400 cc. of urine and was incontinent part of the time. Her systolic blood pressure fluctuated between 84 and 120 mm. and her pulse rate was 150 at first and dropped to 120 beats per minute. Her respiratory distress and stridor increased, and she complained for a while of pain in the chest, but she raised no sputum. Coarse rales were heard throughout both lungs. The tracheal obstruction increased steadily, until breathing finally stopped and could not be restored by artificial respiration. Unfortunately there was no autopsy in this case. The possibility that the large volume of fluid had a deleterious effect on her respiratory symptoms cannot be entirely ruled out but seems unlikely.

The cases cited represent the ones in which the largest volumes of plasma and other fluids were given, considering the limited extent of the surface burns. Some of these patients had minor symptoms of involvement of the respiratory tract, while others had severe injuries; one of them died as a result of these bronchopulmonary injuries. Many other therapeutic measures, including morphine, oxygen and a variety of stimulants, were also used in these cases, of course. Their effects are considered elsewhere.[2a] The chief immediate interest in these cases lies in the fact that it is difficult to attribute any significant part of the respiratory distress or any embarrassment of the circulation to the relatively large amounts of plasma and other fluids used. It cannot be stated categorically, however, that they did not contribute to the inflammatory edema in various parts of the respiratory tract and thus also to the obstructive phenomena that were observed.

COMMENT

The exact cause of the pulmonary lesions in the victims of the Cocoanut Grove fire was not determined. At the time of that disaster, the rapid development and severity of the respiratory symptoms, the diffuse rales heard in the chests of many of the patients and the number of deaths resulting from the pulmonary complications within the first few hours all suggested the possibility of a pulmonary irritant such as phosgene. Interest in that possibility was particularly keen at the time because of the widespread educational campaign then being carried on to acquaint the medical profession and civilian defense workers with the various aspects of gas warfare. In addition there was circumstantial evidence which pointed directly to phosgene as a possible factor. The refrigerant used in the air-conditioning system was probably Freon (dichlorodifluoromethane) which, when exposed to free flame or to very hot surfaces, may decompose and liberate phosgene and hydro-

fluoric acid.[6] An early inspection of the charred remains of the building revealed that the tubing which carried the refrigerant had been severed at a point at which the escaping gas must have been exposed to free flame as it entered the main dining room.[7]

The phosgene theory, as well as others which directly implicated specific poison gases, was discarded after a more complete analysis of the available facts. It seemed more reasonable to assume that the injuries were the result of prolonged exposure to the ordinary gases and fumes which result from the incomplete combustion of the type of furnishings which were to be found in the Cocoanut Grove building. The severity of the injuries seemed to be related to the amount of actual exposure to these fumes and to the flames before the victims got out into the open air. The thick, soot-laden exudate which was found lining the mucous membranes all along the respiratory passages in the fatal case was consistent with that explanation. The symptoms and the roentgenologic and pathologic findings were consistent with a severe laryngotracheobronchitis which, because of the edematous and membranous character of the inflammatory reaction in the tracheobronchial tree, gave rise to obstruction of the air passages, which, in turn, resulted in scattered areas of atelectasis and emphysema.

It is possible, therefore, that the nature of the lesions in the present cases could account for the failure of the large amounts of plasma and other fluids to aggravate the pulmonary symptoms. Indeed this form of therapy may have had a salutary effect on the pulmonary lesion similar to that which it may have on surface burns. From the evidence in the present cases it cannot be stated with any degree of certainty what effect such large volumes of fluid and plasma would have on the pulmonary edema produced by phosgene or by other pulmonary irritants when that is accompanied by extensive surface burns, and especially with "shock" present or impending. Indeed it is not certain that the pulmonary edema of phosgene poisoning, when accompanied by depression of the blood pressure, hemoconcentration and other manifestations of clinical shock, would be aggravated by the administration of proper amounts of plasma and other fluids such as would be indicated in the treatment of shock under other conditions which are not accompanied by pulmonary edema. We are not aware of any convincing evidence to clarify this point, although such evidence may be available but not yet revealed.

6. Holmquist, C. A.: Possible Hazards Resulting from Damage to Refrigerators and Equipment in Case of Bombing, Memorandum M-1746, Office of Civilian Defense, Washington, D. C., 1942.

7. Moulton, R. S.: The Cocoanut Grove Night Club Fire, Boston, Nov. 28, 1942, Boston, National Fire Protection Association, 1943.

SUMMARY AND CONCLUSIONS

The data available concerning the administration of plasma and other fluids to the victims of the Cocoanut Grove fire who were admitted to the Boston City Hospital have been analyzed with particular reference to their effect on complications involving the respiratory tract. When all of these data were considered, and particularly when the effects of the largest volumes given to those who were critically ill were carefully scrutinized, it appeared that pulmonary edema did not occur and that the respiratory complications, in general, were not aggravated as a result of this therapy as it was carried out in these cases.

Dr. Charles C. Lund and the other members of the hospital staff granted us permission to study these cases, and Dr. F. H. Laskey Taylor assisted in the study.

HYPERACTIVE CARDIOINHIBITORY CAROTID SINUS REFLEX

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LOS ANGELES

IT has been known for many years that pressure on the neck over the carotid artery produces slowing of the heart. Parry [1] in 1799 described a retardation of the heart in man by pressure over one carotid artery. Waller [2] in 1862 made similar observations. Czermack [3] in 1866 attributed the slowing of the heart to mechanical stimulation of the vagus nerve. Many observations were reported on the effects on the cardiac mechanism of pressure over the carotid sheaths, and the test was called the vagus pressure test. It was not until 1927, with the publication of Hering's excellent monograph,[4] that it was definitely demonstrated that the vagus nerve was not affected directly but that pressure over the carotid sheath stimulated sensory endings in the carotid sinus, which resulted in reflex cardiac inhibition and other reflex effects.

The brilliant investigations of Hering,[4] Heymans [5] and Koch [6] established the function of the carotid sinus in man. The possibility that abnormal stimulation of the carotid sinus mechanism might give rise to symptoms has been suggested in several reports. Prior to the discovery of the carotid sinus reflex Czermack [3] (1866) noted in himself that pressure over the right side of the neck was liable to cause dizziness and faintness. Hering [4] in his monograph suggests that death from hanging and the knockout blow in the neck, in boxing, might

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1. Parry, C. H.: An Inquiry into the Symptoms and Causes of Syncope Anginosa, Commonly Called Angina Pectoris, Bath, R. Cuttwell, 1799.

2. Waller, A.: Experimental Researches on the Functions of the Vagus and the Cervical Sympathetic Nerves in Man, Proc. Roy. Soc., London **11**:302, 1862.

3. Czermack, J.: Ueber mechanische Vagus-Reizung beim Menschen, Jenaische Ztschr. f. Med. u. Naturw. **2**:384, 1866.

4. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927.

5. Heymans, C.: Le sinus carotidien et les autres zones vasosensibles réflexogènes, London, H. K. Lewis & Co., Ltd., 1929.

6. Koch, E.: Die reflektorische Selbsteuerung des Kreislaufes, Dresden, Theodor Steinkopff, 1931.

be the result of stimulation of the carotid sinus. Gaisbeck[7] (1928) observed fainting and convulsions associated with a hyperactive carotid sinus reflex. Roskam[8] in 1930 described a 52 year old patient who suffered severe and frequent attacks of unconsciousness and convulsions. He demonstrated that pressure over the carotid sinus or stretching the skin over the sinus as in shaving would induce an attack. It was Weiss and Baker[9] (1933), however, who brought wide attention to the clinical significance of the hyperactive carotid sinus reflex. These observers, studying a large group of patients with symptoms of fainting and convulsions and related symptoms, found 15 in whom pressure on the carotid sinus reproduced the symptoms. They described in detail the features of the carotid sinus syndrome. The efferent effects of the carotid sinus sensitivity were divided into three types: (1) cardiac, (2) depressor, and (3) cerebral. The observations of Weiss and Baker have been confirmed by others, and the syndrome is now well established.

In patients whose attacks are frequent and disabling, surgical denervation of the carotid sinus has been performed. The relief of symptoms has not been uniformly successful, and therapeutic failures and incomplete cures have been reported.[10] Favorable results would be anticipated (*a*) if in all cases the clinical manifestations were due solely to the hyperactive carotid sinus mechanism and (*b*) if in all instances surgical therapy eliminated the hypersensitive portion of the reflex. Therapeutic failures could be explained by either (*a*) an improper evaluation of the significance of an abnormal response to carotid sinus stimulation leading to errors in diagnosis or (*b*) an incomplete understanding of the site of hypersensitivity of the hyperactive reflex resulting in the failure of surgical measures to eliminate the underlying pathologic condition.

In the course of pharmacologic studies on the carotid sinus[11] the sensitivity of the reflex was tested routinely over a period of years.

7. Gaisbeck, F., cited by Koch.[6]

8. Roskam, J.: Un syndrome nouveau syncopes cardiaques graves et syncopes répétées par hyperréflectivité sino-carotidienne, Presse méd. **38**:590, 1930.

9. (*a*) Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**:297, 1933. (*b*) Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, ibid. **14**:377, 1935.

10. (*a*) Weiss, S.; Capps, R. B.; Ferris, E. B., Jr., and Munro, D.: Syncope and convulsions Due to a Hyperactive Carotid Sinus Reflex, Arch. Int. Med. **58**:407 (Sept.) 1936. (*b*) Craig, W. M., and Smith, H. L.: The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes, Yale J. Biol. & Med. **11**:415, 1939.

11. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387 (March) 1933; Further Observations on the Effect of Drugs on Induced Cardiac Standstill, ibid. **54**: 111 (July) 1934.

A large number of persons were found who exhibited a pronounced cardiac inhibition on stimulation of the carotid sinus. From this material the following studies were carried out, first, an analysis of the incidence of the carotid sinus syndrome in persons who exhibit a hyperactive response and, second, a study of the site of hypersensitivity of the hyperactive reflex.

INCIDENCE OF THE CAROTID SINUS SYNDROME IN PERSONS WITH A HYPERACTIVE CARDIOINHIBITORY REFLEX

Procedure.—The observations were carried out on ambulant patients who were tested routinely by mechanical stimulation of the carotid sinus. Although both sinuses were frequently tested, the present observations include the response to pressure on the right carotid sinus only, since this usually elicited the more pronounced cardiac inhibition. In the literature the meaning of a hyperactive cardioinhibitory response is frequently rather vague. Some published records show only a moderate cardiac inhibition, interpreted as a hyperactive reaction. In the present study the following were considered as the requirements for a hyperactive response: (1) a cardiac standstill of at least five seconds' duration, (2) cardiac inhibition induced by simple pressure on the carotid sinus without massage of the sinus, and (3) a standstill of equal intensity elicited on several tests. The last was included because in some persons a hyperactive response could be obtained on the first application of pressure; however, the reflex apparently became easily refractory, as on a second application of pressure the intensity of response was greatly diminished. Such reactions were not included in this series.

Of those persons from whom a hyperactive cardioinhibitory response was obtained a careful history was taken with special reference to symptoms considered characteristic of the carotid sinus syndrome. Inquiry was especially made concerning such symptoms as attacks of syncope, convulsions, faintness and dizziness.

The patient was questioned concerning the influence on the development of symptoms of position of the body, movements of the head and neck and pressure on the neck by constricting neckwear. When suggestive symptoms were elicited, the pressure on the carotid sinus was repeated, and a comparison was made of the induced symptoms and those of the spontaneous attacks.

Results.—A cardiac standstill fulfilling the criteria mentioned was induced in 115 patients. The youngest was 30 years and the oldest 81 years of age, the average age being 58.9 years. Table 1 shows the age distribution by decades. There were 98 men and 17 women in this group. The greater frequency of cardiac inhibition with age

has previously been observed (Gilbert,[12] Sigler [13] and Nathanson [14a]). The greater frequency and intensity of the cardiac response in men has also been reported.[14]

Of the 115 patients exhibiting a hyperactive cardioinhibitory reaction 77, or 67 per cent, presented no symptoms suggestive of the carotid sinus syndrome. Of the remaining 38 patients there were 23 whose reactions could be classified as instances of the carotid sinus syndrome with a fair degree of certainty. In 10 patients the manifestations of the carotid syndrome were the chief complaints, while in the remainder these symptoms were secondary and of relatively mild degree. Attacks of syncope were experienced by only 6 patients. Attacks of sufficient severity and frequency to cause serious disability were experienced by only 4. In 1 patient denervation of the left carotid sinus was performed.

The symptoms in most instances were described as attacks of sudden weakness, dizziness or faintness. The sensations were usually

TABLE 1.—*Age Distribution of 115 Patients with a Hyperactive Cardioinhibitory Carotid Sinus Reflex*

Age, Years	Number of Patients
30 - 40	4
40 - 50	14
50 - 60	37
60 - 70	44
70 - 80	15
80 - 90	1

related to changes of position of the body or head. Two patients experienced the symptoms while straining at stool. In each case the subjective sensations were reproducible by pressure on the carotid sinus.

Of especial interest is the group of 15 persons who presented symptoms resembling those of the carotid sinus syndrome but who were excluded for the following reasons: First, some mechanism other than the hyperactive carotid sinus reflex could be demonstrated as a basis for the attacks, and second, the spontaneous attacks did not resemble the symptoms produced by pressure over the carotid sinus. In 5 persons there as a true vertigo associated with nausea and tinnitus, indicative of Ménière's syndrome. The sensations

12. Gilbert, N. C.: The Increase of Certain Vagal Effects with Increased Age, Arch. Int. Med. **31**:423 (March) 1923.

13. Sigler, L. H.: Clinical Observations on the Carotid Sinus Reflex, Am. J. M. Sc. **186**:118, 1933.

14. (*a*) Nathanson, M. H.: Rhythmic Property of the Human Heart, Arch. Int. Med. **72**:613 (Nov.) 1943. (*b*) Sigler, L. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex, Arch. Int. Med. **67**:177 (Jan.) 1941.

following pressure on the carotid sinus had no similarity to the sensations at the time of the spontaneous attacks.

In 4 patients the symptoms of faintness and dizziness were associated with attacks of paroxysmal tachycardia. Two persons suffering anginal attacks noted that a sensation of faintness followed the use of glyceryl trinitrate.

One patient is of particular interest in that he had two types of manifestations, (1) attacks of faintness which could be reproduced by pressure on the carotid sinus and (2) attacks of severe vertigo apparently due to Ménièrès syndrome, which could not be induced by stimulation of the carotid sinus. For 4 persons the diagnosis was neurosis, and the symptoms induced in them did not resemble the spontaneous attacks.

COMMENT

It is apparent that a large proportion of persons possessing a hyperactive cardioinhibitory reflex of the carotid sinus do not exhibit

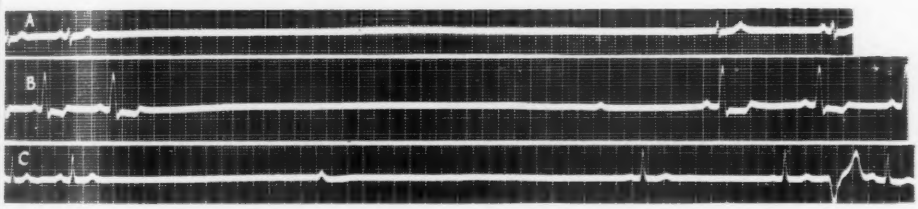

Fig. 1.—*A*, electrocardiogram of patient I. W. showing a cardiac standstill of 8.2 seconds easily induced by pressure on the right carotid sinus. The patient had no symptoms suggestive of the carotid sinus syndrome. *B*, electrocardiogram of patient J. W. showing the effect of pressure on the right carotid sinus for 3 seconds, ventricular standstill of 7.6 seconds induced. The patient had coronary disease but presented no symptoms indicative of cerebral ischemia. *C*, electrocardiogram of patient J. L. showing a ventricular standstill of 7.2 seconds induced by pressure over the right carotid sinus. The patient did not exhibit any symptoms indicative of the carotid sinus syndrome.

the manifestations of the carotid sinus syndrome. A definite distinction must thus be made between the hyperactive carotid sinus reflex, which designates a hyperactive response to stimulation of the carotid sinus, and the carotid sinus syndrome, which designates a clinical condition. There is no satisfactory explanation for the absence of symptoms in many persons and the presence of symptoms in others. The cardiac inhibition was as intense and as easily elicited in the asymptomatic group as in those presenting symptoms (fig. 1). Many persons in whom a prolonged cardiac arrest could be induced consistently with remarkable ease tolerated sudden movements of the head and body and tight neckwear without the slightest discomfort.

A variation in sensitivity to cerebral ischemia might be considered as a possible explanation. It is conceivable that cerebral ischemia is better tolerated by some persons than by others. Such a variation in reaction was noted in the present study. A prolonged cardiac standstill was induced in many instances with relatively minor subjective and objective reactions. In other persons faintness and dizziness followed a cardiac inhibition of only a moderate degree. However, there was no apparent difference as regards the tolerance to the induced cardiac arrest in the group presenting symptoms as compared with the asymptomatic group.

The following is offered as a reasonable explanation for the variation in clinical manifestations in persons who possess a hyperactive reflex of the carotid sinus. The sensory receptors in the carotid sinus are located in the adventitial layer. In this position they are easily accessible to external pressure such as is applied in the carotid sinus test. The ease with which a cardiac standstill and the associated symptoms may be induced by pressure on the sinus is apparently responsible for the general impression that the spontaneous attacks are also induced by external pressure. Weiss and his associates [9] have emphasized such factors as pressure from a tight collar, a blow over a sensitive sinus and changes in position of the head in precipitating attacks. However, these observers stated that in only a few cases did the history clearly indicate a mechanical stimulation of the sinus as a cause of spontaneous syncope. In the present study a definite history suggesting the influence of external pressure was noted for only 1 patient. The symptoms were usually precipitated by a change in the position of the body or a sudden movement of the head. It need not be assumed that such movements stimulate the sensory receptors in the sinus by external compression, since changes in the intravascular pressure may also be brought about in the same manner. The pressure within the carotid sinus, the intrasinal pressure, is the normal physiologic stimulus, and changes in this pressure are transmitted to the sensory receptors. The fact that a history of mechanical stimulation as a cause of spontaneous attacks is infrequent suggests that symptoms result from variations in intravascular pressure rather than from variations in external pressure. The activity of the reflex as elicited by external pressure (the carotid sinus test) is not necessarily an exact measure of the intensity of the response to variations in intrasinal pressure. Sunder-Plassman [15] and Keele [16]

15. Sunder-Plassman, P.: Untersuchungen über den Bulbus carotidis bei Mensch und Tier im Hinblick auf die "Sinusreflexe" nach, H. E. Hering, Ztschr. f. d. ges. Anat. (Abt. 1) **93**:567, 1930.

16. Keele, C. A.: Pathological Changes in Carotid Sinus and Their Relation to Hypertension, Quart. J. Med. **2**:213, 1933.

have shown that arteriosclerotic changes are likely to be pronounced and to occur early in the carotid sinus. It is a definite possibility that the structure of the carotid sinus in some persons is such that changes in intrasinal pressure are easily transmitted to the sensory endings, resulting in cardiac inhibition and the associated symptoms. In other persons (the asymptomatic group) structural abnormalities may be present in the sinus which, acting as a block, prevent variations in intrasinal pressure from stimulating effectively the sensory receptors in the adventitial layer. Spontaneous attacks would occur only in those persons in whom the hyperactive response is elicited by an increase in both external and internal pressure. These variations in the mechanism of the carotid sinus are suggested as a possible explanation for the difference in clinical manifestations in persons who possess a hyperactive carotid sinus reflex.

The realization that a hyperactive carotid sinus reflex may be only incidental and of no clinical significance is of practical importance. An appreciation of this fact will prevent errors in diagnosis and treatment. Four patients of the present series had previously received the diagnosis of carotid sinus syndrome, primarily because a hyperactive carotid sinus reflex could be elicited. Denervation of the carotid sinus was considered. On further study, 1 patient having attacks of amnesia and confusion was found to be suffering from a severe psychoneurosis, and for the other 3 patients the diagnosis was Ménière's syndrome. An important diagnostic point is the ability to reproduce symptoms of the spontaneous attacks by pressure on the carotid sinus. If the induced symptoms do no simulate the spontaneous attacks, some other mechanism should be looked for as a basis for the clinical condition. It is very possible that some of the unsatisfactory results following surgical treatment of the carotid sinus syndrome are due to an uncritical selection of patients.

The Site of Hypersensitiveness of the Hyperactive Cardioinhibitory Reflex.—Early investigators of the carotid sinus reflex [17] attributed the hyperactive response to hypersensitivity of the sensory receptors in the sinus. They concluded that local sclerotic changes were important in that mechanical pressure on a sclerotic plaque would result in a more intense stimulation of these receptors. A hyperirritability of the afferent receptors caused by ischemia of the neural endings subsequent to vascular sclerosis was also considered. More recently Koffler and Alexander [18] also concluded that calcareous deposits in the wall of the carotid artery were responsible for the exaggerated reaction.

17. Hering.[4] Heymans.[5] Koch.[6]

18. Koffler, A., and Alexander, S. F.: Hyperactive Carotid Sinus Reflex Syndrome, New York State J. Med. **40**:1519, 1940.

There is some evidence that the site of hyperirritability may be in other portions of the reflex pathway. Weiss and his associates [9] emphasized the importance of local lesions in or about the sinus. However, these observers also made the following statement: "In the hyperactive state of the reflex, the condition of the efferent end organs as well as the afferent end organ, i. e. the morphological condition of the sinus, plays an important role."

The participation of the efferent end organ, the heart, in the hyperactive response is suggested by several investigations. Before the discovery of the carotid sinus reflex the cardiac slowing which followed pressure over the carotid artery was attributed to direct stimulation of the vagus nerve. The hyperactive response was explained as due to increased sensitivity of the endings of the vagus nerve resulting from pathologic changes in the heart. An exaggerated cardiac response to "vagus pressure" in heart disease was observed by Wenckebach and Winterberg,[19] Daniélopolu and Missirlin,[20] Braun and Samet [21] and others. Braun and Samet [21] also demonstrated an exaggerated cardiac inhibition on stimulation of the vagus nerve in cats following ligation of the left coronary artery. Weiss and Baker [9a] stated that "patients with coronary disease tended to exhibit marked slowing of the heart" on stimulation of the carotid sinus. Sigler [14b] concluded that coronary disease was the condition in which the reflex occurs with the greatest frequency and the highest degrees of response. These observations suggest that the efferent limb of the reflex may be implicated in the hyperactive response.

METHOD AND OBSERVATIONS

In the present study an attempt was made to determine the site of hypersensitivity of the hyperactive cardioinhibitory reflex by a method previously described.[22] The previous report was limited to observations on 1 patient, while in the present study the method was applied to a larger group. The basis of the method is the following: Hering [4] has demonstrated that pressure on the carotid sinus elicits two independent effects: (*a*) a cardioinhibitory effect and (*b*) a

19. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927.

20. Daniélopolu, D., and Missirlin, V.: Excitabilité centrifuge du vague dans les hypertonies générales et les lésions chroniques du coeur: valeur diagnostique et pronostique de l'épreuve du vague dans ces affections, Compt. rend. Soc. de biol. **92**:538, 1925.

21. Braun, L., and Samet, B.: "Vagusdruck" und Koronargefäss: (Ein klinischer und experimenteller Beitrag zur Diagnose und Prognose der Herzkrankheiten), Deutsches Arch. f. klin. Med. **161**:257, 1928.

22. Nathanson, M. H.: Site of Hypersensitiveness of the Exaggerated Sinus Caroticus Reflex, Proc. Soc. Exper. Biol. & Med. **29**:1037, 1932.

vasodepressor effect. The sensory receptors in the carotid sinus and the afferent nerve pathways are the same for both reflexes. There are, however, two separate efferent pathways by way of the vagus nerve to the heart (cardioinhibitory effect) and by way of vasomotor fibers to the blood vessels (vasodepressor action) (fig. 2). The cardiac effect may be eliminated by atropine and the vascular reaction independently observed. Since the afferent endings are common to both reflexes, a pronounced cardioinhibitory effect may be explained by a hypersensitiveness of the afferent receptors if there is likewise a vascular reaction of a comparable degree. On the other hand, the combination of a pronounced cardiac inhibition and a mild effect on blood pressure is strong evidence that the afferent mechanism is not the site of hypersensitivity of the reflex. With this as a basis, persons showing hyperactive cardioinhibitory responses were selected and observations made on the vascular reactions to pressure on the carotid sinus.

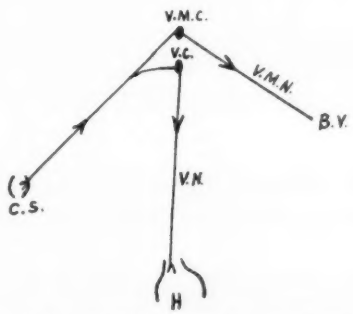

Fig. 2.—Diagram of the carotid sinus reflex pathways. Cardioinhibitory and depressor impulses pass from the receptors in the carotid sinus (*C.S.*) by a common pathway to the vagus (*V.C.*) and vasomotor (*V.M.C.*) centers in the medulla. There are two separate efferent pathways by way of the vagus (*V.N.*) to the heart (*H*), cardioinhibitory reflex, and by way of the vasomotor nerves (*V.M.N.*) to the blood vessels (*B.V.*), depressor reflex.

These observations were carried out on 12 male patients. In each instance a prolonged cardiac standstill of at least six seconds' duration could be elicited repeatedly by pressure on the right carotid sinus. The procedure with each patient was as follows: After the patient had rested in the supine position for fifteen minutes, several readings of the systolic and diastolic blood pressures were made. An electrocardiogram was then taken and the induced cardiac standstill demonstrated graphically. Atropine sulfate, 0.001 Gm., was then administered intravenously. After an interval of five minutes the blood pressure was again taken and the electrocardiogram repeated to determine the effect of pressure on the carotid sinus. In each instance

the cardioinhibitory response was abolished (fig. 3). The depressor reaction could then be observed independently. The blood pressure was then taken before and during the stimulation of the right carotid sinus. Readings were continued until the blood pressure returned to the original levels. Since the degree of reponse depends on the intensity of the stimulus, the duration and intensity of the pressure on the carotid sinus were maintained constant in each experiment. In each instance a fall in systolic pressure followed stimulation of the carotid sinus. The changes in the diastolic pressure were less noticeable. After the administration of atropine, pressure on the carotid sinus produced an average drop in systolic pressure of 15 mm. of

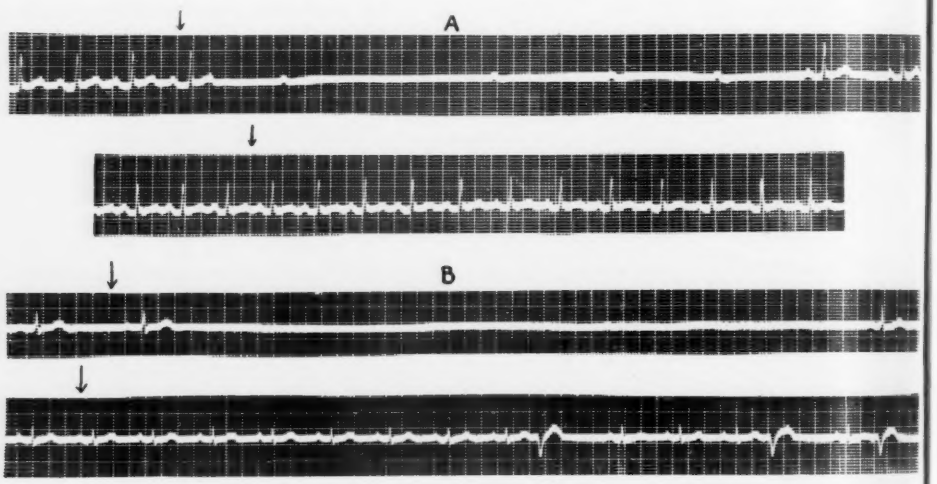

Fig. 3.—*A*, electrocardiogram of J. L.: Upper strip shows ventricular standstill of 8 seconds induced by pressure on the right carotid sinus (arrow). Lower strip shows abolition of standstill after administration of atropine sulfate. Pressure on the carotid sinus after the administration of atropine induced a drop in blood pressure of 8 mm. systolic and 6 mm. diastolic.

B, electrocardiogram of L. R.: The upper strip shows cardiac standstill of 9.4 seconds induced by pressure on the right carotid sinus (arrow). The lower strip shows abolition of standstill after administration of atropine sulfate. Pressure on the carotid sinus after the administration of atropine induced a drop in systolic pressure of 14 mm. of mercury. The diastolic pressure was not affected.

mercury and in diastolic pressure of 4.2 mm. of mercury. The results of these observations are shown in table 2.

Various reports in the literature indicate that the depressor reactions observed in the present study cannot be considered abnormal in degree. Tomanek [23] observed a drop in blood pressure of 9 to 12.5

23. Tomanek, Z.: Carotissinusreflex beim Menschen, Klin. Wchnschr. **7**:898, 1928.

per cent in normal persons. Mandelstamm and Lifschitz [24] demonstrated an average fall in systolic blood pressure of 37 mm. of mercury in elderly patients. Weiss and Baker [9a] in a group of nonhypersensitive elderly persons found a drop in systolic pressure of from 10 to 65 mm. of mercury, with an average of 30 mm. The average fall in diastolic pressure was 25 mm. It is evident that the depressor responses observed in the present study are mild in degree and not at all comparable in intensity to the cardioinhibitory reactions elicited. These results indicate that the afferent pathway may be excluded as the site of hypersensitivity of the cardioinhibitory reflex.

TABLE 2.—*Blood Pressure Responses to Stimulation of the Carotid Sinus After the Administration of Atropine to Persons Who Have a Hyperactive Cardioinhibitory Carotid Sinus Reflex*

Patient	Age	Blood Pressure (Before Atropine), Mm. Hg	After Atropine	
			Before Carotid Sinus Pressure, Mm. Hg	During Carotid Sinus Pressure, Mm. Hg
L. G.	68	118/72	112/60	82/60
L. R.	75	122/84	118/60	104/60
H. K.	65	156/78	140/74	110/62
A. S.	70	116/60	118/62	108/62
H. L.	50	104/72	106/78	100/80
J. S.	72	104/70	102/70	84/62
N. L.	62	120/72	114/70	104/70
L. L.	63	118/82	112/80	102/72
J. B.	68	112/80	120/80	110/68
J. S.	70	130/90	128/90	110/90
J. L.	37	136/74	124/70	116/64
M. P.	62	132/90	130/90	120/78

COMMENT

The afferent pathway having been excluded as the site of hypersensitivity, either the vagus center in the medulla or the efferent path, the vagus nerve, must be considered responsible for the hyperactive response. The evidence strongly favors a hypersensitivity of the vagus nerve. This is supported by the frequent association of a hyperactive carotid sinus reflex with clinical disease of the peripheral end organ, the heart. Also, hyperactivity of the carotid sinus reaction has been produced by experimental damage to the myocardium.[21] In animals and in human beings there is evidence of an increased activity of the vagus nerve with age.[25] It has been shown repeatedly that the cardioinhibitory response to stimulation of the carotid sinus is more frequent and intense in advanced years.[14b,a] An exaggeration of

24. Mandelstamm, M., and Lifschitz, S.: Die Wirkung der Karotissinusreflexe auf den Blutdruck beim Menschen, Wien. Arch. f. inn. Med. **22**:397, 1932.

25. Allbutt, C.: Diseases of the Arteries Including Angina Pectoris, London, Macmillan & Co., 1915. Gilbert.[12]

the cardioinhibitory reflex has been observed after the administration of drugs which sensitize the vagus, such as digitalis,[26] and mecholyl (acetyl-beta-methylcholine).[9]

The localization of the site of hypersensitivity of the carotid sinus reflex is of more than theoretic significance. Surgical denervation of the carotid sinus is a method of therapy for patients having symptoms attributed to a hyperactive reflex. Such therapy by eliminating the afferent receptors should result in a permanent cure if the hypersensitivity was in the afferent pathway. However, it might be anticipated that denervation of the carotid sinus would not insure a consistent and permanent cure if the hypersensitivity was predominantly in the vagus nerve. It is true that by this procedure the chief pathway for afferent impulses is removed and the activity of a hypersensitive vagus nerve thus reduced. However, as is well known with other reflexes, the vagus nerve can be reflexly activated from other sites in the body. Weiss and Ferris[27] reported a vasovagal syncope in which impulses originating in a diverticulum of the esophogus reflexly caused sufficient stimulation of the vagus to produce cardiac standstill. They reported other cases in which a similar vagal reflex originated from the bronchi, pharynx, larynx and eyeball. Capps and Lewis[28] observed instances in which vagal reflexes could be induced by irritation of the pleura.

The carotid sinus is thus but one of a number of sensory areas from which reactions of a similar nature may be produced. The patient with the carotid sinus syndrome still possesses a hypersensitive vagus nerve after denervation of the carotid sinus. Reflex vagal stimulation resulting in symptoms may thus persist, although the possibility is lessened by the elimination of a most important source of afferent stimuli. This might well be the explanation for the variable results following denervation of the carotid sinus. Craig and Smith[10b] followed 12 patients with whom this procedure had been carried out. As to elimination of symptoms of the carotid sinus syndrome, the following were the results: 4 excellent, 1 good, 4 fairly good and 3 failures. The fact that after denervation of the carotid sinus the clinical course was frequently unchanged or only slightly modified suggests that a hypersensitive vagus mechanism continued to be activated from other sensory areas.

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26. Nathanson.[11] Koch.[6] Weiss and Baker.[9a] Ferris, Capps and Weiss.[9b]

27. Weiss, S., and Ferris, E. B., Jr.: Adams-Stokes Syndrome with Transient Complete Heart Block of Vasovagal Reflex Origin, Arch. Int. Med. **54**:931 (Dec.) 1934.

28. Capps, J. A., and Lewis, D. D.: Observations upon Certain Blood-Pressure-Lowering Reflexes That Arise from Irritation of the Inflamed Pleura, Tr. A. Am. Physicians **22**:635, 1907.

SUMMARY AND CONCLUSIONS

1. A study was made of a group of 115 persons in whom a hyperactive carotid sinus cardioinhibitory reflex was elicited.

2. The hyperactive reflex was more frequent in advanced age and in men.

3. Only a small proportion of the persons with a hyperactive reflex exhibited the manifestations of the carotid sinus syndrome.

4. An explanation is offered for the variation in clinical manifestations among the persons showing a hyperactive carotid sinus reflex.

5. A correct evaluation of the significance of a hyperactive reflex is necessary so that errors in diagnosis and therapy may be avoided.

6. Observations are presented which indicate that hypersensitivity of the vagus nerve is the basis for the hyperactive cardioinhibitory carotid sinus reflex.

7. A hyperactive response of the vagus nerve to stimuli from various sensory areas is suggested as an explanation for some therapeutic failures following denervation of the carotid sinus.

SYSTEMIC INFECTION DUE TO TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS)

I. Report of Four Cases and Review of the Literature

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SYSTEMIC infection by Torula histolytica was first clearly recognized by Stoddard and Cutler in 1916.[1] In their exhaustive monograph they reported 2 cases in man and established the criteria for differentiation of Torula histolytica (a term which they introduced) from Blastomycosis hominis and Coccidioides immitis, with which it previously had been confused. The chief means of distinguishing these organisms is by their manner of growth on artificial media; Torula organisms reproduce by budding only; Blastomyces organisms form arthrospores, and Coccidioides organisms form endospores. In clinical practice Torula organisms have been overlooked because of the failure to culture them on suitable media or for sufficiently long periods of time. They have also been mistaken for white blood cells in examination of the spinal fluid. The problem of their identification has been reviewed recently by Holt.[2]

In 1937, Levin[3] reviewed the literature up to that time, summarizing the clinical and pathologic observations. Binford[4] added 14 cases from the literature and his own experience from the time of Levin's review until 1940. In the table these summaries are extended to cover the cases reported from 1940 to the present in accordance with Levin's scheme; they cover a total of 108 cases.

It will be seen that the age incidence of torulosis is rather uniformly distributed over the period of active adult life, and that the disease is approximately twice as frequent in males as in females.

From the Department of Medicine, Indiana University Medical Center, Indianapolis, Ind., aided by the Eli Lilly Research Fund.

1. Stoddard, J. L. and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

2. Holt, R. A.: The Identification of Blastomycoides Histolytica in Three Infections of the Central Nervous System, J. Lab. & Clin. Med. **27**:58-62, (Oct.) 1941.

3. Levin, E. A.: Torula Infection of the Central Nervous System, Arch. Int. Med. **59**:667-684 (April) 1937.

4. Binford, C. H.: Torulosis of the Central Nervous System: Review of Recent Literature and Report of a Case, Am. J. Clin. Path. **11**:242-251 (March) 1941.

The generalized form of infection has increased relatively since the time of Levin's report, and the antemortem diagnosis is being made more frequently. This undoubtedly reflects an increased consciousness of the disease.

Inspection of the figures relative to the duration of the illness and reading of the individual case reports suggest that infections with Torula organisms may follow two courses. The majority of patients will die within six months of the onset of symptoms, but if they survive this initial acute phase they may then live from two to four years. This would suggest that if the patient can overcome the primary attack some form of immunity occurs, or a relative balance between the host and the organism. If this is true, our knowledge up to the present would offer no good explanation for such a phenomenon. Stoddard and Cutler [1] in their original article were unable to demonstrate any consistent response of immunity to the organism. Hoff,[5] in a more recent attempt to produce an immunity in mice by the injection of the killed organisms, could increase their survival time compared to that of normal controls after the injection of virulent organisms; but the inference from his data is that the immunized group all died, also, even though it required a longer period of time. Immunity, if it is considered to be the ability to overcome the disease, has not been demonstrated up to the present time.

Since the involvement of the central nervous system is the most constant feature of systemic torulosis and is invariably the cause of death, the clinical picture is one of a meningitis of slow onset or one of an intracranial neoplasm. Intermittent headache of increasing frequency and intensity is the most frequent initial symptom. This may be followed by vertigo, stiffness of the neck, symptoms of a focal brain lesion, irritability and, ultimately, profound mental disorders. Nuchal rigidity, positive Kernig's sign, ophthalmoplegia and papilledema are the manifestations most constantly observed on physical examination, and focal neurologic signs are frequent. The course is progressively downhill, with a fever seldom above 101 F., to death in coma with respiratory failure. Examinations of the blood and the urine are usually of no diagnostic significance, although the organisms have been obtained in some cases in blood and urine cultures. Examination of the spinal fluid shows it to be under increased pressure; the fluid may be clear, xanthochromic or turbid. The cell counts range from 200 to 800, and there is usually a predominance of lymphocytes. Albumin and globulin are increased, and the sugar may be very low. The organisms may be seen on direct smear as round, gram-positive cells which

5. Hoff, C. L.: Immunity Studies of Cryptococcus hominis (Torula Histolytica) in Mice, J. Lab. Clin. Med. **27**:751-754 (March) 1942.

have doubly refracting walls and reproduce by budding, or they may be found only after culture.

The most constant pathologic lesion found in these cases is the miliary nodule, which both grossly and microscopically resembles a tubercle. In early visceral lesions an abscess consists of an amorphous mass of disintegrating polynuclear and mononuclear white cells and yeast cells surrounded by a loosely organized wall of vascular connective tissue. Throughout the wall is a generalized infiltration of large mononuclear phagocytic cells, which may at times form multinucleate giant cells. In older lesions, whorls of fibroblasts and epithelioid cells surround a homogeneous center in which the yeast cells are ill defined. Giant cells are more frequent at this stage.

In the central nervous system the evidences of tissue reaction are much less. The meninges may show an inflammatory granulomatous process, and the surface of the brain itself may show a zoogleic mass, staining homogeneously and containing numerous yeast cells. In the brain substance monocytic cellular reaction occurs about the larger vessels, suggesting that the organism follows the vessels into the brain, and most parenchymal lesions follow their course. These lesions have the appearance of cysts containing Torula organisms lying free in a cavity of normal brain tissue. Very little if any glial reaction occurs about these cavities.

The mode of infection with Torula histolytica continues to remain obscure. Infections have been reported from all sections of the world and occur in all classes of society. The portal of entry is most probably the lung, as this organ is the second most frequently infected tissue. Thence the infection is probably carried to the other organs by way of the blood and the lymph channels. That it is a true septicemia is further indicated by the work of Wade and Stevenson.[6] When they inoculated white mice intracerebrally, intravenously, intraperitoneally, intratracheally and subcutaneously, they were unable to produce involvement of the central nervous system without visceral involvement, chiefly of lung and kidney and less frequently of liver and spleen. Intranasal inoculation caused a severe rhinitis and sinusitis. Organisms spread out beneath the mucous membrane and beneath the cribriform plate but did not invade the nervous system.

REPORT OF CASES

CASE 1.—J. A. C., a 31 year old white man, was admitted to the medical service of the Robert Long Hospital on April 16, 1933, complaining of severe and persistent headaches of six weeks' duration. The headaches were accompanied with nausea. During this interval he had become increasingly nervous and

6. Wade, L. J., and Stevenson, L. D.: Torula Infection, Yale J. Biol. & Med **13**:467-476 (March) 1941.

reckless, until he was forced to quit working. On April 10, 1933, he had had a generalized convulsion. The past history was irrelevant except for partial deafness in the left ear for twenty years. Five years before the patient's admission this ear had drained for a short time.

General physical examination revealed nothing remarkable. Neurologic examination showed a semistuporous patient who could respond at times but was disoriented as to time and place. Initially the cranial nerves were all intact except for slight blurring of the left disk. Later, definite papilledema developed on the left and the tongue protruded to the left. Nuchal rigidity and positive Kernig's sign were present. Right abdominal, patellar and achilles tendon reflexes were diminished. There was considerable weakness in the muscles on the right.

Urinalysis indicated nothing abnormal. There was slight anemia. Counts of white blood cells ranged from 4,500 to 12,000 with a shift to the left. The pressure of the spinal fluid was constantly elevated; cell counts initially were from 280 to 300, later dropped to 100, with a predominance of polymorphonuclear cells; Pandy's test showed globulin (from 3 plus to 4 plus); sugar was too low to be read on the colorimeter. Yeast cells considered to be Torula histolytica were present.

The patient's course in the hospital was progressively downhill. Attacks of vomiting were frequent, and hiccuping was often troublesome. Repeated spinal punctures were made in an effort to relieve his distress. On April 27, 1933, a left temporal decompression was performed. On May 5, 1933, a left simple mastoidectomy was done. His temperature ranged from normal in the morning to 101 F. in the evening. Death occurred on June 22, 1933, fifty-two days after the patient's admission to the hospital.

An autopsy was performed one hour post mortem. Grossly the meninges appeared hyperemic, with many small grayish masses in the arachnoid and just beneath it. The brain was hyperemic, and there was a soft fluctuant mass in the anterior portion of the left frontal lobe; the lateral ventricles seemed enlarged, and their interior was filled with a mossy substance which later proved microscopically to be yeastlike fungi. An abscess 1 cm. in diameter, full of thick, green pus, was found in the apex of the left lung. Many gray abscesses were seen in the cortex of the kidney. Microscopic sections confirmed the presence of Torula organisms in the abscesses seen grossly. In addition, a single focal, granulomatous lesion containing yeast cells was seen in the adrenal glands.

This case is one of generalized torulosis in which focal neurologic signs predominated clinically. Samples of sputum and cultures from the left mastoid process showed no sign of the organism. The pathologist considered the lung abscess as the probable primary lesion because of the age of the scar tissue present. The duration of the illness was three and a half months.

Case 2.—E. B., a white man, aged 55, was admitted to Robert W. Long Hospital on Jan. 2, 1942, because of dysuria, ulcers on the skin, deafness and headaches. In the early summer of 1941 he began to have intermittent urinary obstruction, pyuria, dysuria and cramping pains in the lower part of the abdomen. Gross hematuria occurred on at least one occasion. In August 1942 he was admitted to Methodist Hospital in Indianapolis, and one month later a transurethral prostatectomy was performed. The tissue obtained was reported to the patient's family as indicative of carcinoma of the prostate. Ten days after discharge he was readmitted in uremic coma. By November 10 he had recovered sufficiently

to be discharged. At about this time he begun to suffer very persistent headaches, and the skin lesions were first noted. These began as a large papule with a surrounding area of erythema. In a short time the elevated portion became covered with vesicles, which were later replaced with a tenacious crust. The first lesion appeared on the neck, and others soon followed on the face, scalp, upper part of the trunk and right wrist. The headaches were limited to the temporal area and were greater on the left side. After the onset of his headaches he became deaf in the right ear, and in the middle of the following December he suddenly lost the hearing of his left ear.

General physical examination indicated nothing abnormal except for the skin lesions previously described. Neurologic examination showed the cranial nerves to be normal except for slight papilledema, considerably diminished hearing by both air and bone conduction, slight right hemiparesis, and a staggering gait.

A biopsy of one of the skin lesions showed a microscopic picture which was considered consistent with the diagnosis of histoplasmosis of Darling. Urinalyses showed the specific gravity to vary from 1.004 to 1.012, with a faint trace of albumin, pus cells and many red cells. Hemograms showed a slight anemia and white cell counts up to 11,800 with a shift to the left. Pressure of the spinal fluid was 85 mm. of water. Examination of the spinal fluid revealed 31 cells, globulin 3 plus by the Pandy test, sugar 23 mg. per hundred cubic centimeters, protein 250 mg. per hundred cubic centimeters and yeast cells. Blood cultures and specimens of sputum also contained yeast cells. Roentgenologic examination of the chest showed accentuation of the lung markings in both hilar areas with no definite consolidation.

The patient's course was ingravescent, with death occurring on March 21, 1942. The final clinical diagnosis was histoplasmosis.

Postmortem examination performed three hours after death showed grossly the skin lesion previously described; large, white, granulomatous lesions in the right lung, the largest of which measured from 2 to 4 cm.; an annular nodule around the left ureter; numerous small white nodules in both kidneys, and enlarged mesenteric lymph nodes containing white material similar to that described in other tissues. Microscopic examination revealed small spherical yeastlike fungi in the lungs, kidneys, adrenal glands, skin, prostate, urinary bladder, mesenteric lymph nodes and meninges. The cultural characteristics of these organisms fulfilled the criteria for Torula histolytica. No evidence of prostatic carcinoma was found.

COMMENT

This case of systemic torulosis is unusual in that visceral symptoms were dominant and in that the involvement of the central nervous system was slight. The diagnosis through biopsy of histoplasmosis of Darling undoubtedly confused the clinical picture, and the paucity of gross evidence of involvement of the brain probably was responsible for the pathologists' not obtaining more detailed studies in an attempt to explain the neurologic findings. While involvement of the kidney is frequent, both clinically and experimentally, this is probably the first case in which genitourinary involvement was the presenting symptom. The previous diagnosis of carcinoma of the prostate is difficult to evaluate in view of the serious abnormalities discovered in the lower

urinary tract at autopsy. Duration of the disease was approximately ten months.

CASE 3.—E. G., a 42 year old white man, was admitted to Robert W. Long Hospital Oct. 25, 1944. Six weeks previously he had begun to have very severe generalized headaches, which soon were accompanied with nausea and vomiting. For five weeks photophobia and diplopia had been present. A staggering gait and stiffness of the neck had been noted for approximately one week. The patient had been employed as a molder for seventeen years. Two years previous to the onset of his present illness he had quit work because of increasing weakness, fatigue and shortness of breath. At that time a diagnosis was made of silicosis. He attempted to work at lighter jobs, beginning in February 1941, but was forced to quit in June. He had had a cough productive of tenacious, gray sputum for a number of years, and after quitting work in June, he was found to have tubercle bacilli in his sputum. Significant physical abnormalities observed on general examination were limited to the thorax. The chest was emphysematous in shape, and excursions were slightly increased on the left. Both apexes were slightly dull, and bronchial breath sounds and a few crepitant rales were heard in the left apex. Neurologic examination showed moderate opisthotonus, nuchal rigidity, choked disks (2 D.), left ophthalmoplegia, a negative Romberg sign and staggering, apparently because of weakness.

Urinalyses were within normal values. Hemograms showed normal red blood cell elements, and the highest white blood cell count was 10,100, with a shift to the left in the differential counts. Spinal fluid pressure was 300 mm. of water, cell counts from 8 to 10, sugar 49 mg. per hundred cubic centimeters initially and too low to be read terminally, protein 139 mg. per hundred cubic centimeters and yeast cells in all specimens. Urine and blood cultures both were positive for yeast cells. All of these cultures were proved to be Torula histolytica. Specimens of sputum were repeatedly positive for acid-fact bacilli. Roentgenologic examination of the chest revealed conditions considered to be indicative of advanced silicotuberculosis.

Treatment consisted of saturated solution of potassium iodide, 11 drops (11 grains [0.715 Gm.]) three times a day and sulfadiazine in doses adequate to maintain a level in the blood of approximately 10 mg. per hundred cubic centimeters. The patient's course was downhill, characterized by almost intractable headaches and persistent vomiting. Neurologic conditions observed remained unchanged. Death occurred on November 18.

Autopsy performed four and a half hours post mortem revealed numerous gray, shotty, calcified nodules throughout both lungs, adhesions binding both lungs to the wall of the chest and a cavity some 10 cm. in diameter in the left apex; the meninges appeared thickened and opaque. Microscopic examinations showed silicotuberculosis and yeast cells in the lungs, yeast cells in the spleen and tuberculous splenitis, yeast cells in the glomeruli of the kidneys, yeast cell granulations in the adrenal glands, perivascular yeast cell granulations throughout the brain and a yeast cell meningitis.

COMMENT

While the silicotuberculosis in this patient was sufficiently extensive to be ultimately fatal, we believe that his case may justifiably be classified as another case of generalized torulosis. Sulfadiazine and iodides were given without avail in an effort to alter the course of

his disease. The ten week course is characteristic of the fulminating form of the disease.

Case 4.—C. S., aged 44, has been admitted six times to Indiana University Medical Center. The first of these was in November 1943. The onset of his illness was in February 1938, when he had progressively increasing occipital headaches, which later also involved the frontal area. He was treated for sinusitis, but with the onset of fever in April 1938 a diagnosis of meningitis was made, and he was hospitalized for three weeks. During this period diplopia and deafness of the right ear developed. After he returned home he continued to suffer from headache and backache, and his family noted some personality changes.

Because of his failure to improve he was referred by his local physician, Dr. G. F. Schmidt, to Mayo Clinic in August 1938. Neurologic examination by Dr. F. A. Carmichael revealed "anosmia, bilateral, and an increase in the tendon reflexes, slightly more so on the right side throughout. The abdominal reflexes also were present, and there were no signs referable to the pyramidal tract in either the upper or the lower extremities. There was a distinct tremor of the arms and legs bilaterally. There was no cervical rigidity or tenderness to percussion over the head or spine. No bruits were audible, but there was slight tenderness to palpation in the left posterolateral cervical region." To exclude the possibility of an intracranial mass an encephalogram was made. "There was an abnormal amount of air in the subarachnoid spaces with a secondary dilatation of the ventricular system without shift. The picture was that of an extensive degenerative lesion." The spinal fluid was yellow in color, the reaction to the Wassermann test negative, the total protein 80 mg. per hundred cubic centimeters, the Nonne reaction positive, the cell count 175 and the colloidal gold curve 5553210000. No cultures were made. Serologic reactions of the blood were Kline 3 plus, Kahn negative and Kolmer negative. "A roentgenogram of the chest revealed scattered miliary calcification, probably of no significance; other conditions were normal. The sinuses of the head and the sella turcica were normal on roentgenologic examination." Because of the history of a positive reaction to the Wassermann test and of treatment for syphilis in the past, further therapeutic tests were advised. In January 1939 his home physician stated that he had shown definite improvement but was still moody and nervous.[7]

The patient was ultimately able to return to work on a farm, but by April 1943 he was experiencing so much difficulty in walking and so much pain in his back that he was forced to stop working. His diplopia had receded soon after his initial attack of meningitis, but the deafness had persisted. He had gradually acquired a staggering gait, and he now experienced difficulty in stopping or turning after he had walked a short distance. He also had difficulty in expressing himself. There was no difficulty in pronunciation, but rather one of choosing the right word.

Physical examination on his first admission, on Nov. 25, 1943, revealed nothing remarkable except with respect to the nervous system. The left pupil was larger than the right, and both reacted to light and showed accommodation. No constriction of the visual fields was present. A slight pallor in both optic disks was observed. Air conduction of sound was absent, and bone conduction was less in the right ear. The ear drum was normal. There was a coarse tremor of the tongue, which deviated to the left. The palate and the uvula deviated to the right. There was hemiparesis of the right side, including the face. Reflexes of the tendons were active and equal. No pathologic reflexes were present.

7. Montgomery, H.: Personal communication to the authors.

Sensory examination revealed nothing abnormal. Slight ataxia was shown by the reaction to the finger to nose test. There was a negative Romberg sign. A coarse tremor of the intention type was present in the upper extremities. The patient's gait was propulsive; he experienced difficulty in stopping and turning and a tendency to veer to the right on walking with the eyes closed. The sensorium was clear, but the patient was suspicious and surly in nature.

On laboratory examinations, a urinalysis and a hemogram showed nothing abnormal. Serologic reactions of the blood were negative. The pressure of the spinal fluid was 230 mm. of water. The white cell count was 122, with 5 polymorphonuclear cells and 95 per cent lymphocytes. Pandy's test showed globulin 4 plus; sugar was too low to be read on the colorimeter; there were 268 mg. of protein per hundred cubic centimeters; reaction to the Wassermann test was negative, and there was a gold curve of 5555553310. After seven days' incubation, yeast cells were observed which, after further examination, were considered to be Torula histolytica.

Roentgenologic examination showed the chest to be normal except for numerous calcified parenchymatous deposits, measuring from 1 to 3 mm. in diameter, scattered throughout both lung fields. Roentgenograms of the skull and the mastoid processes were considered to show nothing abnormal.

Before additional examinations could be made the patient became very dissatisfied and signed his own release from the hospital.

The patient was persuaded to return to the hospital for further study on Feb. 21, 1944. On reexamination at that time, the patient's condition was found to be unchanged. Torula organisms were found in urine cultures but were absent in repeated sputum, blood and stool cultures. Cultures from washings of the maxillary sinuses also were negative. The spinal fluid remained the same except for some increase in the total protein. Roentgenologic examinations of the accessory nasal sinuses revealed considerable thickening of the lining membrane of the left antrum and some clouding of the frontal sinuses, particularly on the right. The ethmoid cells, sphenoid sinus and right antrum appeared relatively free from pathologic conditions. Complete gastrointestinal roentgenograms, taken after a barium sulfate meal and a barium sulfate enema, showed stomach and intestines to be normal. Examination of the urinary tract by excretory urography revealed normal kidneys, ureters and bladder.

On March 9, 1944, the patient was placed on sulfadiazine therapy and a level in the blood of 8 to 14 mg. of sulfadiazine per hundred cubic centimeters was maintained until his discharge on April 11, 1944. At the time of discharge he seemed considerably improved. His hemiparesis was almost gone, the ataxia less noticeable and his gait more certain. Subjectively, his headaches were less and he was more cheerful. The last examination of the spinal fluid, made the day before discharge, revealed that the fluid still was positive for Torula organisms, however.

He was seen as an outpatient on May 11, 1944, and, because of a recurrence of symptoms, was placed on a six week course of sulfadiazine therapy under the supervision of his local physician, Dr. Irvin H. Scott, of Sullivan, Ind. While under this therapy the patient ceased to have headaches, but his backache persisted and he still had difficulty in walking, especially at night.

He was readmitted to the hospital on June 26, 1944, and given 15,000 units of penicillin intramuscularly every three hours from June 27 to July 7. Penicillin was given intrathecally in doses of 20,000 units on June 27 and 29 and July 1. No Torula organism was found in the spinal fluid withdrawn before each intrathecal injection, but otherwise the spinal fluid remained unchanged.

He was again admitted to the hospital on Sept. 11, 1944, for reexamination. At that time he stated that he suffered little from backache and that his walking had continued to improve. Neurologic examination now showed nothing abnormal except for deafness in the right ear, slight ataxia on the finger to nose test, and a tendency to veer to the right while walking. Spinal fluid culture was negative for Torula, but the cell count was 128 with 99 per cent lymphocytes, Pandy's test indicated globulin (4 plus), and sugar was too low to be read.

When seen as an outpatient on Nov. 9, 1944, the patient had resumed light work about the house and had no subjective complaints. He was given saturated solution of potassium iodide and instructed to take 30 drops three times a day, increasing the dose by 1 drop a day until he was taking 50 drops three times a day.

He continued to do well until February 1945, when he began to notice increasing difficulty in walking and a tendency to propulsion. Because of the recurrence of symptoms he was readmitted to the hospital on March 19, 1945. Spinal fluid culture of March 22 was positive for Torula organisms. Treatment consisted of intramuscular doses of 20,000 units of penicillin every four hours from March 19 to April 4 and intrathecal doses on March 21 and 27 and April 4. This was followed by sulfadiazine from April 5 to April 15. The spinal fluid still contained Torula organisms on March 21, but none was present after two weeks' incubation in a specimen obtained March 26.

When seen on May 19, 1945, after the course of penicillin and sulfadiazine, he was feeling better and had gained in weight. A slightly staggering gait and the tendency to veer to the right while walking were again noted. Left temporal and right occipital headaches still were present. There was some general weakness of motor power and a coarse tremor of the hands. Spinal fluid culture still was positive for Torula histolytica.

COMMENT

It may be stated definitely that this patient is suffering from meningoencephalitis and a probable renal infection, inasmuch as Torula organisms were isolated from the urine. His initial improvement after the use of sulfadiazine was striking, but on subsequent courses of that drug he has failed to show similar gain. The lack of response to intrathecal and intramuscular doses of penicillin is comparable to the experience of Harford and his colleagues.[8] The duration of illness of seven years is the second longest recorded case in the literature, and though his spinal fluid still was positive at his last visit to the clinic, there has been no gross change in his condition in the past year.

SURVEY OF THE CURRENT LITERATURE

The 7 cases in the current literature in the table in which the duration is considered unknown deserve further comment, since these concern patients still living at the time of publication of their reports. The most important of these is case 4 of Reeves, Butt and Hammack.[9] The known duration of this 21 year old woman's illness is at

8. Harford, C. G.: Martin, S. P.; Hagemann, P. O., and Wood, W. B.: Treatment of Staphylococcic, Pneumococcic, and Other Infections with Penicillin, J. A. M. A. **127**:325-329 (Feb. 10) 1945.

9. Reeves, D. L.: Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and the Central Nervous System, Arch. Int. Med. **68**:57-79 (July) 1941.

least seven years and eight months, the longest on record. She is suffering from involvement of the central nervous system plus a pulmonary lesion with a draining sinus through the wall of the

Summary of Cases According to the Schema of Levin [3]

	Levin	Binford 1940	Beck-Voyles 1945	Total
Sex of patient:				
Male	39	9	23	71
Female	20	4*	13*	37
Age distribution in years:				
Under 10	1	2	1	4
10-19	6	1	4	11
20-29	9	3*	9	21
30-39	9	3	8	20
40-49	15	1	4	20
50-59	16	1	7	24
60-69	2	2	2	6
Not stated	2	0	0	2
Duration of illness in months:				
0-1	3	3	3	9
1	6	0	1	7
2	10	3	6	19
3	9	1	5	15
4	8	0	5	13
5	3	1	2	6
6	3	2	1	6
7	1	0	1	2
8	2	0	0	2
9	1	0	1	2
10-12	1	0	1	2
13-24	3	0	1	4
25-36	5	0	1	6
37-48	0	1	1*	2
49-60	0	1	0	1
61-72	1	0	0	1
Unknown	4	0*	7	11
Organs involved including the central nervous system:				
Lungs	9	4	7	20
Generalized	8	1	6	15
Kidney	2	2	8	12
Spleen	1	1	3	5
Adrenal glands	1	1	5	7
Abdominal nodes	1	0	3	4
Peribronchial nodes	1	0	1	2
Tonsil	3	0	0	3
Subcutaneous tissue	2	0	2	4
Skin	5	0	1	6
Central nervous system only	30	4*	20	54
When diagnosed:				
Post mortem	23	8	6	37
Ante mortem	37	5*	29*	71
How diagnosed:				
Antemortem cultures only	10	4*	26*	40
Biopsy of the brain ante mortem	2	1	5	8
Postmortem histologic sections	22	0	4	26
Cultures and postmorten histologic sections	26	0	1	27

* These cases appeared in Binford's review, but were advanced to the next column in duplicate with correction in number.

chest. When last seen by Dr. Hammack [10] in December 1944, she still was having difficulty in walking and with her vision. Her spinal fluid contained no Torula organisms on culture, but the cell count was

10. Reeves, D. L.: Butt, E. M., and Hammack, R. W.: Personal communication to the authors.

29 and the protein 200 mg. per hundred cubic centimeters. She has received iodides to the limit of her tolerance from time to time and the Torula antigen prepared by Dr. Kreuger of the University of California (Berkeley) more or less continuously.

The case of the 9 year old girl reported by Marshall and Teed [11] is another instance in which a person suffering with Torula meningitis is known to be living at the present time. Although Dr. Teed is now unavailable, being overseas as a commander in the United States Navy, an inquiry concerning this child was answered by his wife.[12] She states that the child "is living, in school, active and well, save for occasional headaches." The onset of her illness was in December 1941. She was treated with mastoidectomy and repeated courses of sulfadiazine. She had been unable to attend school and apparently had been considered of subnormal intelligence before her treatment. This may have been due to her deafness; nevertheless, since her treatment she has been able to resume a relatively normal life four years and four months since the onset of her symptoms.

Case 3 of Burger and Morton [13] does not properly belong in a review of systemic Torula infection since the infection was limited to the tissues of the thigh. It is included, however, for the sake of completeness in the review of the literature. This patient was treated by disarticulation of the femur and there has been no recurrence. Case 5 necessitated revision of Binford's review, since it is a follow-up of Magruder's case 3.[14] This case is that of a 22 year old Negress who died at her home after an illness of three years and four months.

Our own case 4 is one of those in which the duration of the illness is considered unknown. Follow-ups were not obtained on the remaining 3 cases. Dr. E. C. Toone,[15] who reported the case of an 18 year old Negress, is now overseas as a major in the United States Army. This patient was seen during the acute phase of her illness in March 1938. When last seen, in September 1940, her spinal fluid still contained Torula histolytica. Major Toone [16] referred us to her family

11. Marshall, M., and Teed, R. W.: Torula Histolytica Meningoencephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy; Preliminary Report, J. A. M. A. **120**:527-529 (Oct. 17) 1942.

12. Marshall, M., and Teed, R. W.: Personal communication to the authors.

13. Burger, R. E., and Morton, C. B.: Torula Infection: A Review and Report of Four Cases, Surgery **15**:312-325 (Feb.) 1944.

14. Magruder, R. G.: Report of Three Cases of Torula Infection of the Central Nervous System, J. Lab. & Clin. Med. **24**:495-499 (Feb.) 1939.

15. Toone, E. C., Jr.: Torula Histolytica (Blastomycoides Histolytica) Meningitis: Report of a Case with Recovery, Virginia M. Monthly **68**: 405-407 (July) 1941.

16. Toone, E. C.: Personal communication to the authors.

physician for information concerning her later course, but we have received no reply from him in response to our inquiries.

The remaining 2 cases are those of a 27 year old man reported by Farrer [17] and a 32 year old man reported by Dickmann, Veppo and Negri.[18] Farrer's patient was convalescent from the acute phase of his illness at the time of reporting, but he still had symptoms. The symptoms of the patient reported by Dickmann and his colleagues had been present since September 1941. On Feb. 2, 1942, an occipital craniotomy disclosed a tumor on the left cerebellar hemisphere. Torula organisms were found in his spinal fluid on February 26 and were identified in the tumor mass removed by operation. He was released against the advice of the surgical staff on March 4, 1942.

SUMMARY

1. A summary of the literature, including all reported cases from Binford's review [4] in 1940 to the present date, has been presented according to Levin's schema.[3]

2. The pertinent clinical and laboratory observations have been emphasized.

3. It is suggested that the course of infection may be fulminating or chronic and that if the patient survives the initial acute phase, the duration of illness may be two to three years.

4. The pathogenesis remains unexplained.

5. Four additional cases with observations at autopsy have been presented.

17. Farrer, R.: Torula Meningitis, Roy. Melbourne Hosp. Clin. Rep. **12**:31-32 (Dec.) 1941.

18. Dickmann, G. H.; Veppo, A. A., and Negri, T.: Torulopsis del sistema nervioso central (cerebelo) de fornea tumoral, Rev. neurol. de Buenos Aires **7**: 347-360 (Oct.-Dec.) 1942.

SYSTEMIC INFECTION DUE TO TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS)

II. Effect of Chemotherapeutic Agents in Experimentally Produced Infections

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AND
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BECAUSE of the apparent improvement following treatment with sulfadiazine observed in the case reported by Marshall and Teed and in our own case 4 my colleague and I determined to test the efficacy of this substance in experimentally produced infections with Torula organisms. Since iodides have been a time-honored remedy in fungus infections on what seems to be a purely empiric basis, it was thought that they also should be subjected to experimental evaluation.

PROCEDURE

Four species of animals were used, rats, rabbits, guinea pigs and dogs. All species were inoculated at the same time with emulsions of Torula histolytica originally obtained from the spinal fluid culture of case 4. These organisms had been subcultured on Sabouraud's dextrose agar and were suspended in sterile isotonic solution of sodium chloride before injection. The number of organisms injected was standardized by a preliminary enumeration of organisms per cubic millimeter in a standard blood-counting chamber. The emulsion was diluted and the organisms counted in the same manner as are red blood cells. The number of organisms injected in each species is indicated in the table. Dogs and rabbits were given intraveneous injections; guinea pigs, intracardial and rats, intraperitoneal.

Each species was divided into four groups designated as the control, iodide, sulfadiazine and sulfadiazine and iodide sections. After a period of about two weeks, when the animals began to appear ill, treatment was started with the drugs indicated by their section. The drugs were dissolved in the drinking water and placed in the cages for the animals. Potassium iodide was supplied in the amount of 6 Gm. per liter, and sulfadiazine 4 Gm. per liter. The dose of iodides would correspond to 1 grain per pound (243 mg. per kilogram), which is the usual dose per day for a man in fungus infections. Levels of sulfadiazine in the blood were obtained at weekly intervals and were

From the Department of Internal Medicine, Indiana University Medical School and Medical Center, aided by the Eli Lilly Research Fund.

maintained between 12 and 18 mg. per hundred cubic centimeters. When the animal took insufficient sulfadiazine in the drinking water an additional amount was given in tablet form to maintain this level.

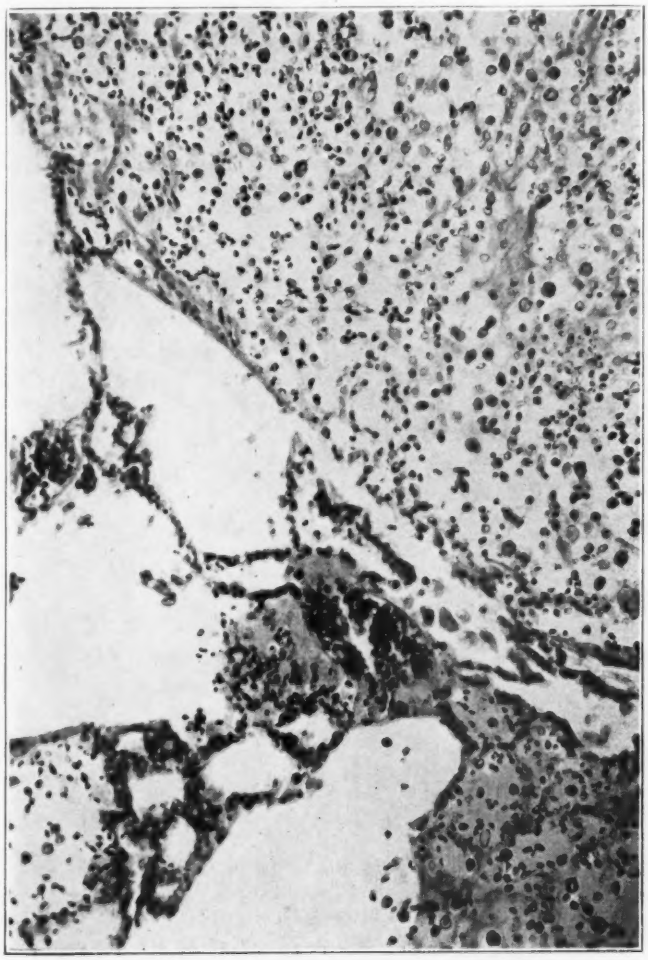

Fig. 1.—Photomicrograph of rat lung showing almost total loss of normal structure and total infiltration with Torula organisms without exudative phenomena and with little fibrosis (× approximately 250).

Determinations of sulfadiazine levels were made by an adaptation of the method of Bratton and Marshall [1] devised by Dr. T. Makovsky

1. Bratton, C. A., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:437 (May) 1939.

of the Department of Clinical Pathology of the Indiana University Medical Center. This is truly a micromethod, requiring only 20 cu. mm. of blood for the determination. The reagents required are 12 per cent trichloroacetic acid, 0.1 per cent sodium nitrite, 0.5 per cent ammonium sulfamate, and 0.1 per cent ethylenediamine.

PROCEDURE

1. Draw up 20 cu. mm. of blood into a micropipet.
2. Discharge in 1 cc. of distilled water in a Wassermann tube. Agitate the blood and rinse the pipet by drawing the fluid up and discharging it several times.

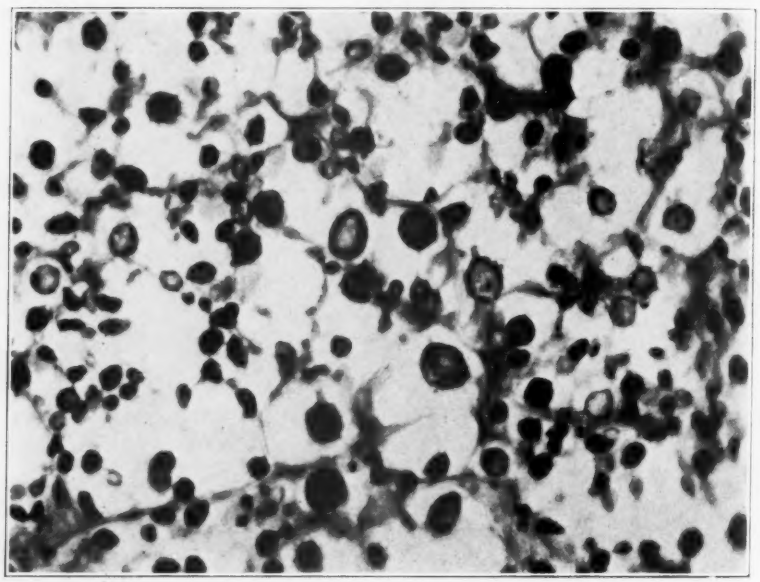

Fig. 2.—Lung section showing the morphology of Torula histolytica (× 800).

3. Allow hemolysis for about one minute.
4. Precipitate the protein by adding 0.6 cc. of 12 per cent trichloroacetic acid. Mix and allow to stand for three minutes.
5. Centrifuge at high speed for four minutes to pack the precipitate well.
6. Pipet off 1 cc. of the supernatant fluid with a volumetric pipet. Discharge this into a Wassermann tube.
7. Add 0.1 cc. of 0.1 per cent sodium nitrite; mix well by shaking; let stand three minutes.
8. Add 0.1 cc. of 0.5 per cent ammonium sulfamate, mix well by shaking and let stand two minutes.

9. Add 0.1 cc. of 0.1 per cent ethylenediamine; mix well; let stand two minutes.
10. Compare with a standard in a microcolorimeter.

A standard containing 20 mg. of sulfadiazine per hundred cubic centimeters is treated in exactly the same manner as the unknown.

On the death of the animal and at the conclusion of the experiment a postmortem examination was performed immediately and representative sections were taken for microscopic examination. Sections were stained with eosin-hematoxylin and by Gram-Weigert methods.

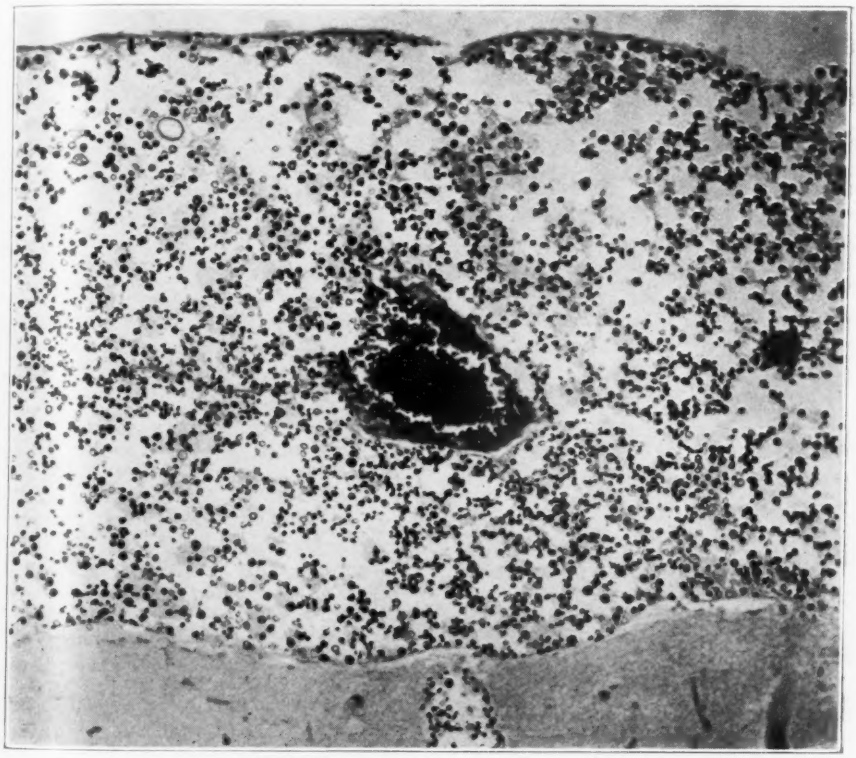

Fig. 3.—Photomicrograph of dog brain showing an area of meningitis. There are few exudative phenomena and little phagocytosis or fibrosis (× 200).

RESULTS

Results of these experiments are presented in the table. This table is so arranged that opposite each species of animal is stated the

number of organisms with which the animal was inoculated and the day on which treatment was begun. The numbers beneath each group indicate the duration of life after inoculation, and "present" or "absent" indicates the presence or absence of Torula histolytica in microsections obtained from postmortem examination of the animals.

The Effect of Potassium Iodide, Sulfadiazine and Sulfadiazine and Potassium Iodide on Torula Organisms

Dog; Inoculum—Fifteen Million Organisms. Treatment Started Fifteenth Day After Inoculation

Control	Potassium Iodide	Sulfadiazine	Sulfadiazine and Potassium Iodide
18 Present	23 Present	39 Present	34 Absent
71 Absent *	24 Absent	24 Present	34 Present
71 Present *	78 Present	82 Absent *	39 Absent
71 Absent *	82 Absent *	39 Present	40 Present

Rabbits; Inoculum—Seven Million Organisms. Treatment Started on Twelfth Day After Inoculation

Control	Potassium Iodide	Sulfadiazine	Sulfadiazine and Potassium Iodide
23 Present	27 Present	29 Present	24 Present
73 Present *	44 Absent	79 Absent *	29 Present
73 Absent *	73 Present *	79 Absent *	37 Absent
79 Absent *	79 Present *	79 Absent *	88 Absent *
	79 Present *	79 Absent *	88 Absent *
		79 Present *	

Guinea Pigs; Inoculum—Three Million Organisms. Treatment Started on Eleventh Day After Inoculation

Control	Potassium Iodide	Sulfadiazine	Sulfadiazine and Potassium Iodide
5 Absent	14 Present	18 Present	14 Present
9 Absent	15 Present	26 Present	24 Present
10 Absent	22 Absent	32 Present	50 Present
23 Absent	23 Absent	35 Present	53 Present
24 Present †	38 Present	36 Present	58 Present
31 Present	47 Present	38 No slides †	63 Present *
32 Present	49 Present	44 Present	63 Present *
33 Absent	52 Present	46 Present	63 Present *
34 Absent	61 Present	48 Present	63 Absent *
		63 Present	

Rats; Inoculum—Two Million Organisms. Treatment Started on Thirteenth Day After Inoculation

Control	Potassium Iodide	Sulfadiazine	Sulfadiazine and Potassium Iodide
28½ Present	20 Present	35 Present	20 Present
36 Present	33 Present	51 Present	32 Absent
50 Present	36 Present	56 Present	33 Present
56 Present	40 Present	57 Present	39 Present
86 Absent *	43 Present	64 Present	56 Present
86 Absent *	46 Present	65 Present	61 Present
86 Absent *	46 Present	69 Present	64 Present
86 Present *	64 Present	77 Present	69 Present
86 Present *	69 Absent	81 Present	75 Present
86 Present *	70 Present	86 Present *	86 Present *
86 Absent *	86 Present *	86 Absent *	86 Present *
	86 Present *		

* Killed.

† No microsections.

COMMENT

Reference to the table quickly indicates that the drugs given had no beneficial effects with respect to the morbidity and the mortality among the experimentally infected animals. In fact, many of the control animals had a better course and less evidence of infection at the time of death than the treated groups. My colleague and I do not feel that this

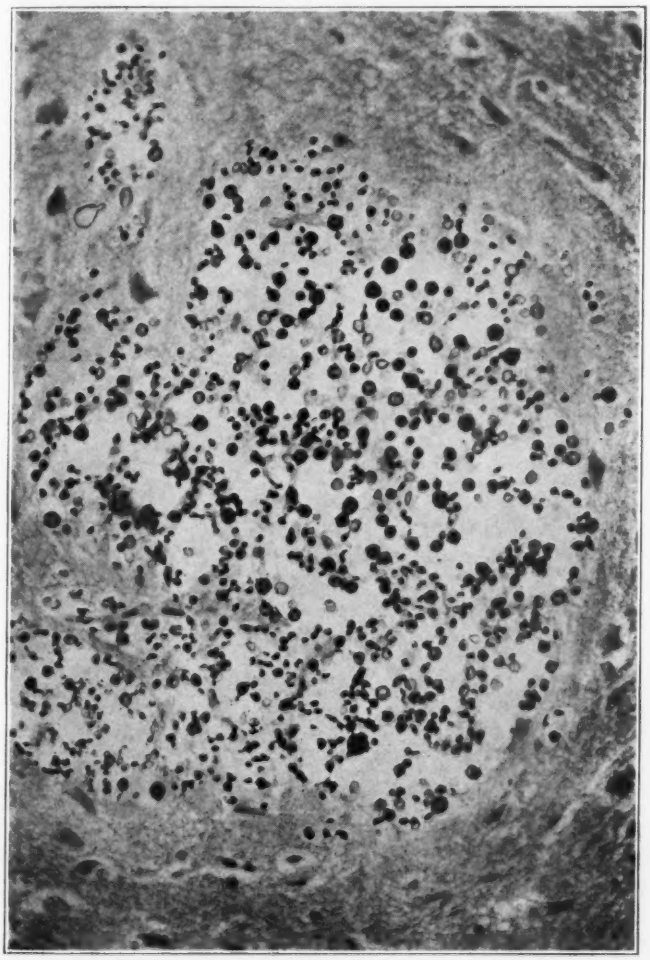

Fig. 4.—Photomicrograph of dog brain showing a small focal lesion not associated with the vascular system. Here may be noted budding Torula organisms, phagocytosis and the apparent disintegration of the cortical substance either because of lysis or because of spreading of the cortical substance by substances produced by the organism (× approximately 250).

difference is due to any deleterious effects of the drugs used. In the animals treated with sulfadiazine, anuria did not occur, and there was no microscopic evidence of renal damage of the type associated with the presence of sulfonamide toxicity. In the more susceptible animals

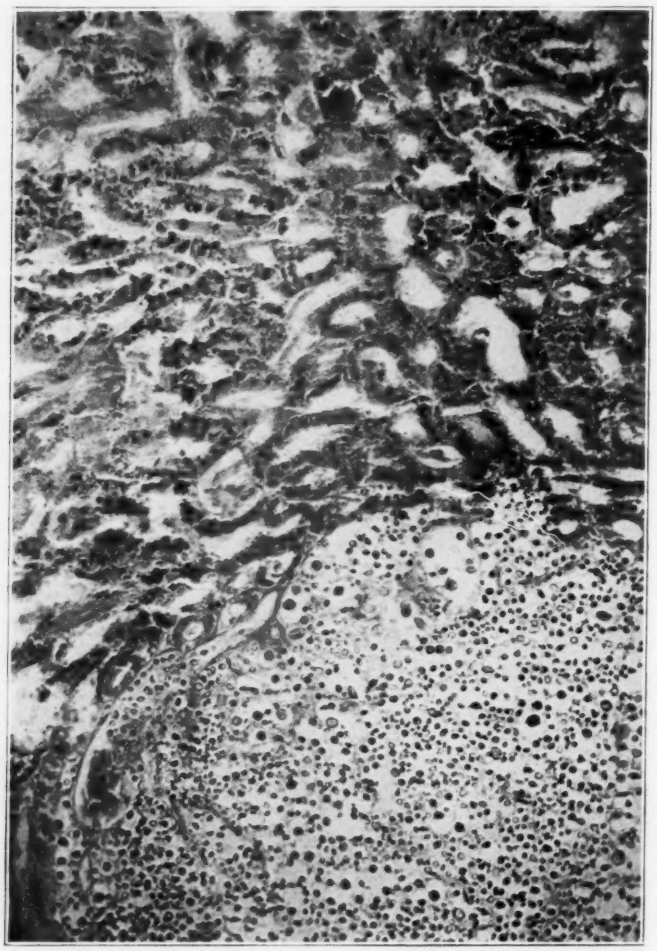

Fig. 5.—Photomicrograph showing a well localized lesion of the renal cortex (× approximately 250).

the mortality rate was actually higher because of infection with Torula organisms, and fewer animals had to be killed at the termination of the experiment in the treated groups. The only exception to this was the

guinea pig section treated with both sulfadiazine and iodides. This might give rise to some speculation as to the undesirable effects of the drugs used on the course of the infection, even though the dose was a subtoxic one.

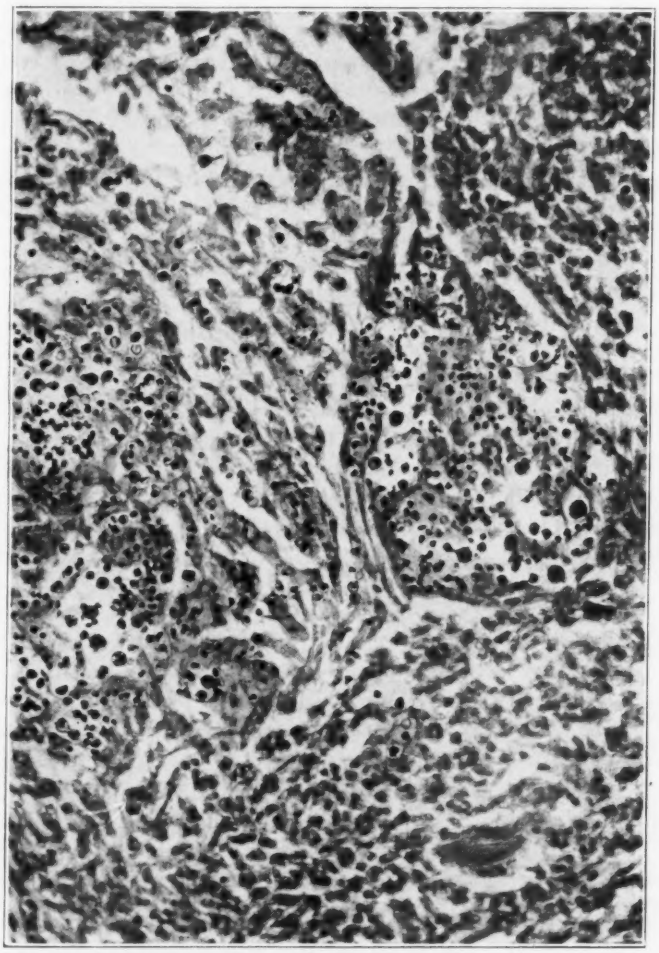

Fig. 6.—Photomicrograph of the spleen of a guinea pig demonstrating Torula lesions (× approximately 250).

It might appear that the inoculum was not great enough in less susceptible animals, since many of them had to be killed to terminate

the experiment or had no microscopic evidence of infection with Torula organisms.

It was not our aim to produce immediate death, but rather a subacute infection similar to that clinically seen. Jones and Klinck [2] recently reported a similar study of the effects of sulfadiazine in experimental infection of mice with Torula organisms. Their results coincided with our own in that there was no difference between the treated and the control groups. They also tested the effects of penicillin, and again there was no difference between the control and the treated groups. Their experiment differs from ours in being more acute in type, the inoculant being adjusted to produce death in twelve and a half days.

Penicillin was not used as a treatment because it was not available in sufficient quantity at the time these experiments were conducted. Neither was the injection of killed organisms or other Torula antigens tested since we feel this already had been adequately investigated by Stoddard and Cutler [3] and more recently by Hoff.[4]

In comparing the pathologic aspects of the lesions of those animals treated with potassium iodide, sulfadiazine and potassium iodide and sulfadiazine with those of the lesions of the animals in the control groups, it was impossible to find any evidence that the drugs used altered the reaction of the body to the organism. Reaction of the tissue with the exception of that of the central nervous system, was confined to a defensive fibrosis with few or no exudative phenomena. The reaction was granulomatous in nature, characterized by the formation of nodules of various sizes composed of fibrous tissue whorls with or without caseation necrosis or hyaline degeneration, epithelioid cells, infiltration of small, round cells occasional giant cells and Torula organisms. Lesions of this type were seen in the lungs, spleen and kidneys, and to a lesser extent in the liver, heart and peritoneum. In the lung a lesion not previously described also was seen. The parenchyma of the lung was totally destroyed, and fibrous tissue encasing myriads of Torula organisms was all that remained.

In the central nervous system the reaction had a different aspect. The Torula organisms seemed to lie in small lacunas. Grossly these spaces were filled with a mucinous substance, possibly a part of the end products of parastic growth, as suggested by Reeves, Butt and

2. Jones, S. H., and Klinck, G. H.: Torula Histolytica (Cryptococcus Hominis) Meningitis: Case Report and Therapeutic Experiments, Ann. Int. Med. **22**:736 (May) 1945.

3. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, Jan. 31, 1916.

4. Hoff, C. L.: Torula Studies of Cryptococcus Hominis in Mice, J. Lab. & Clin. Med. **27**:751 (March) 1942.

Hammack.[5] The infection of the brain and spinal cord was a generalized one involving the deep brain substance, the perivascular spaces and the meningeal coverings of these organs. Any one or all of these lesions may appear simultaneously, which would substantiate the criticism of Freeman's classification [6] by Longmire and Goodwin.[7] The lesions may represent the lytic process, as suggested by Stoddard and Cutler, or the spreading of the brain substance by a mucinous material, as suggested by Reeves, Butt and Hammack.[5] Glial reaction was not remarkable about the lesions in the brain substance. In the meninges the process may be localized or generalized. There was an increase in fibrous tissue with a tendency to the formation of granulomatous tissue accompanied with an infiltration of small round cells. The vascular system of the meninges was congested in nearly all cases. Giant cells, so often reported, were very seldom seen and did not seem to be a prominent part of the pathologic picture.

SUMMARY

1. Experimental studies were conducted on animals infected with Torula histolytica and treated with potassium iodide and sulfadiazine and a combination of the two drugs.

2. The results of this experiment did not indicate any beneficial effect exerted by the drug employed.

5. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and the Central Nervous System, Arch. Int. Med. **68**:57 (July) 1941.

6. Freeman, W.: Torula Meningoencephalitis: Comparative Pathology in Nineteen Cases, Tr. Am. Neurol. A. **56**:203, 1930.

7. Longmire, W. P., Jr., and Goodwin, F. C.: Generalized Torula Infection: Case Report and Review with Observations on Pathogenesis, Bull. Johns Hopkins Hosp. **64**:22 (Jan.) 1939.

ROLE OF HISTAMINE AND ACETYLCHOLINE IN THE MECHANISM OF HEAT ALLERGY

Report of Studies on a Soldier

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INSTANCES of heat allergy, while not common, are not new. Duke [1] in 1925 grouped all hypersensitivities to cold, heat, pressure and light under the term "physical allergy." He introduced the term to indicate an altered reactivity to physical agents. It has been proposed that physical agents release a histamine-like substance in the tissues and that this, in turn, produces subsequent allergic phenomena. However, it has become increasingly apparent that histamine alone is unable to account for all these phenomena. In recent years there have been a number of investigations which tend to show that the chemical substance that mediates allergy is acetylcholine. This belief has been fostered by the fact that some allergic manifestations can be produced by certain cholinergic drugs. For example, acetylcholine chloride in doses of 30 to 40 mg. will precipitate an attack of asthma in a susceptible patient. Encouraging results have been obtained from the use of small doses of the drug in the treatment of asthmatic patients. Grant, Pearson and Comeau [2] showed by experimental evidence that the urticaria produced by emotion, exercise and warming the body was probably due to a release of acetylcholine in the skin, induced by stimulation of the efferent nerve fibers. Liberation of the H substance from the cells of the skin was, in turn, produced.

It is our purpose not to review all the literature on this complex subject but to report certain observations. Our conclusions are essentially in agreement with those of Grant and his co-workers.[2]

Recently it was our fortune to see a soldier with a characteristic physical allergy to exercise and heat. We were afforded an opportunity to study this patient and to obtain some experimental data. The results have led us to believe that the allergic phenomena of the kind observed

1. Duke, W. W.: Physical Allergy: Preliminary Report, J. A. M. A. **84**:736 (March 7) 1925.

2. Grant, R. T.; Pearson, R. S. B., and Comeau, W. J.: Observations on Urticaria Provoked by Emotion, by Exercise and by Warming the Body, Clin. Sc. **2**:253, 1936.

in this patient are based on more than one chemical substance. It was impossible to reconstruct a pure histamine allergy. Similarly, we were unable to demonstrate a pure acetylcholine reaction. The mechanism is complex, and we feel that an acetylcholine-like reaction and a histamine-like reaction are probably both responsible and act together (fig. 1). The following case report and experimental data will clarify what we mean by this concept.

REPORT OF A CASE

This patient was first seen on sick call on March 17, 1945 by one of us (G. A. P.) in an army dispensary. He presented the picture of shock. He had been inducted on March 3, 1945 and had had only one week of basic training when he was brought to the dispensary. At this time his face was flushed and

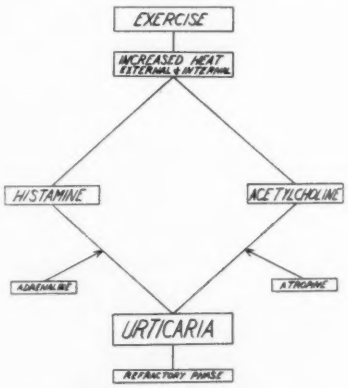

DIAGRAM ILLUSTRATING A PROPOSED MECHANISM OF PHYSICAL ALLERGY SEEN IN OUR PATIENT

Fig. 1.—Illustration of a proposed mechanism of physical allergy seen in our patient.

his lips were cyanotic; there was a circumoral pallor, and generally he was so weak that he had to be assisted into a chair. His temperature was 97.6 F.; his blood pressure was 80 systolic and 60 diastolic; his pulse rate was 100 per minute, and his respiration rate ranged between 20 and 25 per minute. A most striking feature was the dermatologic picture. Over his body there were numerous large wheals and a generalized urticaria. Behind his right ear there was a large edematous swelling, which was about the size of a small hen's egg. Two injections of 1:1,000 solution of epinephrine hydrochloride (0.4 cc.) fifteen minutes apart gave prompt relief, the urticaria subsiding completely in forty-five to sixty minutes.

The history of the present illness was interesting. For the past two years this patient had experienced approximately two episodes of hives a month, breaking out practically all over his body whenever he did any heavy work and became "heated." The rash consisted of wheals varying in size from that of a peanut to as large as that of a walnut. Each attack averaged one to two hours and

subsided spontaneously. There was an intense itching associated with the urticaria, starting usually in the perineal region. On being questioned, the patient stated that he believed that he perspired somewhat less than other people. He also stated that he never noticed a rash while sitting quietly in a hot room regardless of the outside temperature. It seemed that exertion was necessary for its precipitation. There was no relation of the urticaria to any particular food or drug or to contact with any known substance.

His past history was important in that he had moderately severe asthma as a child between the ages of 3 and 7 years. Even in recent years, when an infection developed in the upper part of his respiratory tract he frequently experienced a tightening sensation in his chest, but he did not refer to these

Fig. 2.—Dermographia. (United States Army Signal Corps photograph.)

attacks as those of asthma. In his family history, both his maternal grandmother and his mother had bronchial asthma, and his mother also had an urticarial condition similar to that of her son. The patient stated that his mother had had episodes of hives following exertion for the past ten to fifteen years.

Physical examination between attacks revealed a cooperative 18 year old youth. He was husky, had a ruddy complexion and bright red hair, was well proportioned and definitely did not appear to be of the apprehensive type. He was 6 feet (183 cm.) tall and weighed 185 pounds (84 Kg.). His skin revealed a mild dermographia (fig. 2), but no urticaria was observed between attacks. The blood pressure was 132 mm. systolic and 78 mm. diastolic, and the pulse rate was 76 per minute. The remaining part of his examination revealed essentially normal conditions. A roentgenogram of the chest showed no abnor-

malities of the heart or lungs. The blood sedimentation rates varied from 12 to 19 mm. in one hour (normal, less than 10 mm.). The white blood cell count was 9,850, with a differential count of 48 per cent neutrophils, 38 per cent lymphocytes, 7 per cent monocytes, 3 per cent eosinophils and 4 per cent basophils. The red blood cell count was 5,440,000, and an estimation of hemoglobin revealed 18 Gm. per hundred cubic centimeters of blood. The formation of the red blood cells was normal. A white blood cell count and a differential count, which were repeated later, showed 6,850 white corpuscles, with 51 per cent neutrophils, 38 per cent lymphocytes, 1 per cent monocytes, 8 per cent eosinophils and 2 per cent basophils. The Kahn reaction of the blood was negative. The amount of calcium in the blood was 10.8 mg. per hundred cubic centimeters. A basal metabolism study on two occasions gave readings of —18 and —14 per cent. Two gastric analyses after ingestion of 7 per cent ethyl alcohol on a fasting stomach revealed no free hydrochloric acid. The fasting blood sugar content was 85 mg. per hundred cubic centimeters. A glucose tolerance test showed normal values.

CLINICAL AND EXPERIMENTAL STUDIES

1. *Effect of Physical Agents.*—(*a*) Heat: On March 31, 1945 the patient was subjected to external heat by means of two bakers of eight infra-red radiators each. The environmental temperature was brought up to 115 to 120 F. At the end of ten minutes the patient was perspiring. At the end of twenty minutes he was perspiring moderately and was warm. Pruritus began to be noticeable in the perineal and inguinal regions. At the end of thirty minutes there was profuse perspiration, and urticarial wheals began to be evident all over the body. The face was flushed, grade 4, graded on the basis of 1 to 4. There was a distinct circumoral pallor. The oral temperature rose to 99.8 F. In another five minutes the urticaria was as severe as it had ever been in the patient's experience. The blood pressure remained in the region of 110 systolic and 66 diastolic but the pulse rate became elevated to 104 beats per minute. After another ten minutes the urticaria was maximal. The attack subsided in about one hour.

On April 27, 1945 our patient, together with 2 control patients, was subjected to a warm environment, the temperature starting at 70 F. and gradually increasing to 100 F. The patients were seated in a quiet room. The purpose of this experiment was to see whether our patient's sweating mechanism was functioning normally. To determine the degree and distribution of the sweat pattern the colorimetric technic of Silverman and Powell[3] was used. It was noted that all 3 patients showed normal palmar sweat responses. Within five minutes (room temperature 75 F.) dark stains, indicative of sweating, were visible over the finger tips and palms. At this time no demonstrable sweating was seen over the rest of the body. However, at the end of half an hour (room temperature 83 F.) both control patients, but not the allergic patient, were showing generalized sweating (extremities, chest, neck). The sweating of the 2 controls kept increasing as the environmental temperature was raised. In the meantime, our allergic patient was free of any evidence of sweating, except for the palms, soles and axillas and slightly on the forehead. At the end of two and three-quarter hours, when the temperature outdoors reached 98 F., our patient broke out rather suddenly in generalized body sweating. At this period the intensity and the distribution of the sweat pattern were equal in all 3 patients.

3. Silverman, J. J., and Powell, V. E.: A Simple Technic for Outlining the Sweat Pattern, War Med. **7**:178 (March) 1945.

Our patient under experimental conditions demonstrated a definitely diminished response in generalized body sweating. Under prolonged or intense stimulation, however, a normal response was obtained. Palmar sweating was perfectly normal.

(*b*) Local Heat: On April 5, 1945 the left forearm and arm were immersed in water having a temperature of 110 F. for ten minutes. There was no effect locally on the skin and none on the blood pressure or pulse rate. No urticaria was produced.

Fig. 3.—*A*, patient before exercise; *B*, patient after exercise. (United States Army Signal Corps photograph.)

On April 6, 1945 a test tube of hot water was placed on the skin of the left forearm. After ten minutes there was no evidence of local urticaria, itching or general reaction.

Application of heat over a localized area was unsuccessful in producing an urticaria. It should be noted, however, that we were dealing with local stimuli of insufficient strength to affect the general body temperature.

(*c*) Exercise: On March 20, 1945 and on twelve other occasions on different days, the patient was asked to run for a period of fifteen minutes. During each exercise he covered approximately 2,500 yards (2,200 meters). At the end of that time and within the succeeding ten minutes, it was noticed that a generalized urticaria appeared, associated with considerable pruritus and wheals varying in size from that of a match head to that of a thumb nail. The face became noticeably flushed and swollen (fig. 3*B*), and there was an intense erythema over the neck, shoulders and chest. In addition, there was a characteristic circumoral pallor. The pulse rate and blood pressure were elevated but were within normal limits. Later, after the eruption occurred, the blood pressure dropped to as low as 88 systolic and 50 diastolic. This usually occurred about fifteen to thirty minutes after the eruption became maximal. In approximately one to one and one-half hours the urticaria as well as the pruritus disappeared entirely, and the circulatory system returned to normal.

Studies on the refractory phase. Study after one hour: On April 4, 1945 the patient was exercised for fifteen minutes, and an urticaria developed as described previously. One hour later the patient was again exercised, but no eruption occurred over the body. It appeared as though the patient was in a refractory phase.

Study after three hours: On April 10, 1945 the patient was exercised again in the usual manner, and afterward the skin broke out with typical urticaria. Three hours later he was again exercised in a similar fashion, but this time the skin did not break out in wheals. Apparently the patient was still in a refractory phase, during which it was impossible to provoke an urticarial reaction by the stimulus of exercise. A white blood cell count with a differential count was taken before and after the first exercise. The results are shown below:

	White Blood Cell Count	Differential		
		Polymorphonuclears	Lymphocytes	Eosinophils
Before exercise	10,600	45%	50%	5%
After exercise	16,000	47%	47%	2%

and 2% monocytes and 2% basophils

Apparently the production of the urticaria is not associated with a rise in the eosinophilic cells.

At the height of the urticarial reaction following exercise, a photograph was taken, showing the type of response (fig. 4). A photograph of the skin was taken before exercise for the sake of comparison (fig. 5). Figure 3 is a composite picture showing more of the body before and after exercise performed on another occasion.

Study after five hours: On April 20, 1945 the patient was exercised again in the usual fashion, and subsequently the typical urticaria, pruritus, facial cervical and shoulder flush were observed. In addition, the scrotum and penis became swollen. Five hours later he was again exercised. He had a facial flush after this exercise but only slight pruritus and a few scattered wheals. The latter were mild but definite over the chest, abdomen and shoulders.

Apparently it is possible in five hours to reproduce the urticaria in this patient, but it is not possible to do so during the absolute refractory period of three to four hours following a typical urticarial response induced by exercise. The urticaria induced at the end of five hours was

mild, indicating that the patient may have been in a relative refractory period at the time.

(*d*) Cold: On April 3, 1945 the patient was taken inside a large refrigerator, the temperature of which was between 48 and 50 F. He was kept in there for twenty minutes. No external changes occurred, and no urticaria and no pruritus were noticed after exposure to this environment.

On April 12, 1945 ice cubes were applied to the skin of the right forearm for one minute. No unusual reaction and no wheals occurred as are found to occur in patients allergic to cold.

Fig. 4.—Urticaria after exercise. (United States Army Signal Corps photograph.)

This patient showed no evidence indicating allergy to cold.

(*e*) Pressure: On numerous occasions we were able to demonstrate the response of the skin to stroking with a blunt object. A typical dermatographic response became evident within three to five minutes, demonstrating the triple response of Lewis, that is, the white line, then the wheal and the flare about the zone of stimulataion.

2. *Gastric Analyses.*—On March 22, 1945, 100 cc. of 7 per cent ethyl alcohol was introduced into the patient's fasting stomach. No free hydrochloric acid was produced.

On March 27, 1945 another 100 cc. of 7 per cent ethyl alcohol was introduced into the fasting stomach, and again no free hydrochloric acid was obtained. A gastric analysis immediately after exercise failed to show any free hydrochloric acid one-half hour after the urticaria was induced.

On March 29, 1945 histamine phosphate given intravenously (1:250,000) and subcutaneously (1 mg. per cubic centimeter) brought forth free hydrochloric acid up to as high as 60 units and the total acids up to 65 units.

On March 30, 1945 an attack of generalized urticaria was induced by exposure of the patient to radiant heat for one-half hour as previously described. Gastric

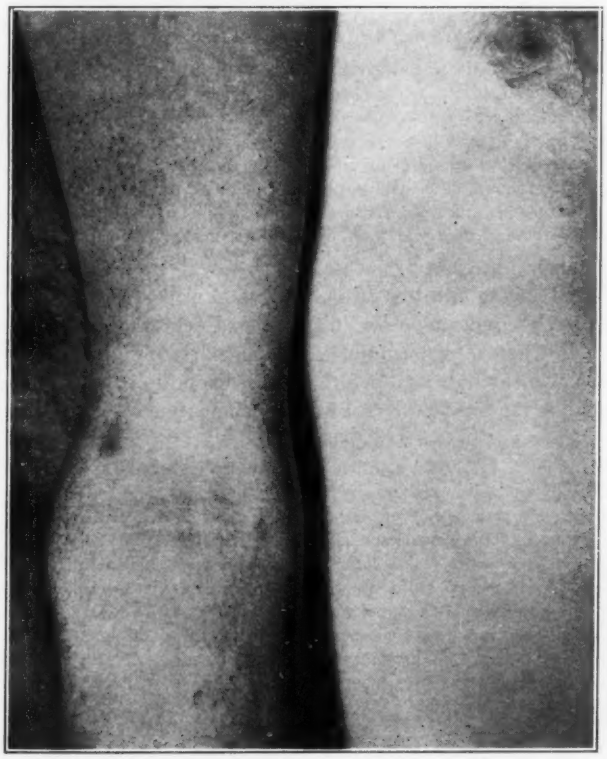

Fig. 5.—No urticaria before exercise or heat. (United States Army Signal Corps photograph.)

analyses for one hour after the eruption failed to reveal the presence of any free hydrochloric acid. Specimens were taken at fifteen minute intervals.

Alcohol, exercise and heat failed to evoke a free hydrochloric acid response. Histamine phosphate, however, gave a prompt response. This problem will be further discussed under "Histamine."

3. *Effect of Drugs.*—Intradermally: A small amount of histamine phosphate (0.10 cc. of a solution containing 1 mg. per cubic centimeter) was injected

intradermally into the skin of the forearm. Within fifteen minutes a typical wheal with pseudopod formation became evident, surrounded by a zone of erythema 2 to 3 inches (6 to 7.6 cm.) in diameter. The wheal was 1 by 1.5 cm. in diameter. The pseudopod portion was about 0.5 cm. long.

Subcutaneously: Four-tenths cubic centimeter of the same histamine phosphate solution produced little effect on the patient. It caused a slight rise in the gastric acids, bringing out free hydrochloric acid, as described under gastric analysis. A slight wheal and some erythema occurred about the site of the injection, but no systemic response was noted.

Intravenously: On March 31, 1945 an intravenous injection of histamine phosphate (1:250,000 solution) was given at a rate of 170 to 200 drops per minute. A total of 200 cc. of the solution (histamine phosphate in isotonic solution of sodium chloride) was given in about twenty minutes. A typical histamine flush of the face, neck, shoulder and upper part of the chest occurred. Around the mouth was a pronounced pallor. No urticaria was observed. The blood pressure did not fall appreciably, although the pulse became accelerated to approximately 100 beats per minute. At the height of the injection—i. e., at the maximal rate of flow—the patient complained of a moderate headache. Specimens of gastric juice were collected at regular intervals, and they showed increasing amounts of free and total hydrochloric acid.

Apparently the gastric mucosa was rather resistant to stimulation, ethyl alcohol having failed on two occasions to provoke free hydrochloric acid. In such circumstances a diagnosis of achlorhydria would have been made. The use of histamine subcutaneously or intravenously as a diagnostic agent is indicated before such a diagnosis is considered. The latter route is the most powerful way of stimulating the gastric mucosa.

Refractory Phase Study (Histamine): On April 18, 1945 the patient was given 250 cc. of a 1:250,000 solution of histamine phosphate at a rapid rate of 105 to 200 drops per minute. The systolic blood pressure did not fall more than 8 to 10. No urticaria developed, but there did appear a pronounced erythema on the face, neck, thorax, abdomen and upper extremity. This erythema showed up at first in little spots which later coalesced to form a generalized reddening of the skin. A circumoral pallor was noted. A moderate headache developed.

After the injection was completed, the patient was exercised in the usual fashion for fifteen minutes. Subsequently an urticarial response was induced, but it seemed to be not so prominent as under ordinary exercise. The eruption was about 75 per cent as prominent over the chest and abdomen as that which develops after exercise only.

The injection of histamine phosphate intravenously before exercise may have had a slight inhibitory effect on the development of subsequent urticaria.

(*b*) Epinephrine: On April 11, 1945 epinephrine hydrochloride, 0.4 cc. of 1:1,000 solution, was injected subcutaneously just before exercise was begun, and seven minutes later a similar quantity was injected midway during the exercise. At the end of the exercise period of fifteen minutes, the patient was observed for nearly an hour. No urticaria, pruritus or any kind of allergic response usually seen after exercise in this patient was observed. The blood pressure was observed to rise to 170 mm. of mercury systolic just after exercise, but this dropped in three minutes to 135 mm. of mercury. The pulse rate remained around 112 beats per minute for fifteen minutes following the exercise.

Epinephrine injected before and during exercise prevented the development of urticaria following exercise.

(*c*) Ephedrine Sulfate: On April 22, 1945 the patient was given ephedrine sulfate, 45 mg. by mouth every four hours for four doses. The patient was then exercised in the usual fashion for fifteen minutes. A typical outbreak of urticaria developed.

Ephedrine sulfate in the dose and frequency employed apparently was ineffective in preventing the urticarial outbreak.

(*d*) Atropine Sulfate: On April 7, 1945 the patient was given 1/75 grain (0.8 mg.) of atropine sulfate subcutaneously. He was then exercised for fifteen minutes in the usual fashion. The drug did not prevent the breaking out of the urticaria, but the rash appeared to be definitely milder. The drug did not prevent the facial flush or the circumoral pallor. Following the exercise the blood pressure was observed to fall to 90 systolic and 66 diastolic, but the pulse rate remained elevated. There was little sweating. The oral temperature became elevated to 100.4 F.

On April 9, 1945 the patient was given a stronger dose of atropine sulfate (1/50 grain [1.2 mg.]) and then exercised as before. This time the breaking out of the urticaria was delayed for half an hour, and when it did come it was minimal. No sweating was observed, but there was a facial flush and mild pruritus. The oral temperature rose to 101 F. The blood pressure rose no higher than 120 systolic and 65 diastolic, and the pulse rate rose as high as 160 immediately after exercise. The mild urticaria disappeared almost completely at the end of fifty minutes.

Atropine sulfate had a definite inhibitory effect on the production of urticaria following exercise.

(*e*) Pilocarpine: The patient was given 1/12 grain (5 mg.) of pilocarpine hydrochloride on April 12, 1945, and the effect was observed systemically. There was no effect on the blood pressure or pulse. The face became warm and flushed; salivation and perspiration were produced, but no urticaria or pruritus was noted. There was a slight fall in the oral temperature. Twenty-five minutes after the injection of the drug, when it appeared that no urticaria was going to develop, a new drug called Furmethide,[4] whose action is similar to that of acetylcholine, was given in a dose of 5 mg. subcutaneously. Seventeen minutes later a definite mild urticaria was observed, the wheals being of about pinhead size. This drug also produced some tightness in the chest, some rales, sweating, salivation, lacrimation, urination and a pronounced facial flush. The wheals started fading out in about thirty to forty minutes.

It is possible that the effect of the pilocarpine had not worn off completely and that when Furmethide was given the combined effect of the two drugs was able to provoke an urticarial response, for, as reported in subsequent paragraphs, Furmethide alone on other occasions failed to bring out any urticaria.

4. Furmethide is chemically related to acetylcholine and is the proprietary name for furfuryl trimethyl ammonium iodide. This drug was supplied by Smith, Kline & French Laboratories, Philadelphia.

(*f*) Furmethide (furfuryl trimethyl ammonium iodide): On April 21, 1945 the patient was given 5 mg. of Furmethide alone subcutaneously, and the effect was observed. The pulse rate was increased from 68 to 100, but there was no effect on the blood pressure. Increased warmth, flushing of the face, lacrimation, pronounced sweating, urination of 400 cc. and scrotal and facial pruritus were noted. No urticaria was observed.

Furmethide alone did not produce urticaria.

(*g*) Furmethide and Histamine: On April 16, 1945 it was thought on the basis of the previous studies that the injection of both histamine and Furmethide might bring out the urticaria. Therefore, 0.4 cc. of histamine phosphate (1 mg. of histamine per cubic centimeter) was given subcutaneously along

Fig. 6.—Region of right shoulder, demonstrating urticaria produced by simultaneous injection of histamine phosphate and Furmethide.

with 2.5 mg. of Furmethide. After an interval of fifteen minutes, when no urticaria was observed, another 2.5 mg. of Furmethide was given, followed by another dose of 0.4 cc. of histamine phosphate ten minutes later. Within ten minutes of the last injection an urticaria began to be evident and progressed in extent until it became similar to that produced by exercise or external heat.

On April 19, 1945 the same drugs were used as in the previous experiment, but this time 0.4 cc. of histamine phosphate and 5 mg. of Furmethide were injected simultaneously into opposite arms. There developed tightness in the chest, flushing of the face, watering of the eyes, sweating of the hands and face and a moderate headache. In about ten minutes following the injection an urticaria began to develop over the body, which increased, the wheals coalescing and becoming larger. At this period there was considerable pruritus in the

perineal, cephalic and shoulder regions. It required about half an hour for the rash to come out to its maximal extent, and when it did it compared favorably with the generalized eruption produced by exercise alone (fig. 6). Unfortunately, the photograph shows the poorest result obtained.

On April 18, 1945 the same two drugs were used in a control patient (nonallergic) in exactly the same manner as described in the experiment of April 16, 1945. No effect was observed on the blood pressure; the pulse rate became somewhat elevated, and the oral temperature fell from 98.4 to 97.8 F. There were considerable sweating and flushing of the face, as well as sweating of the palms. At no time was any urticaria produced.

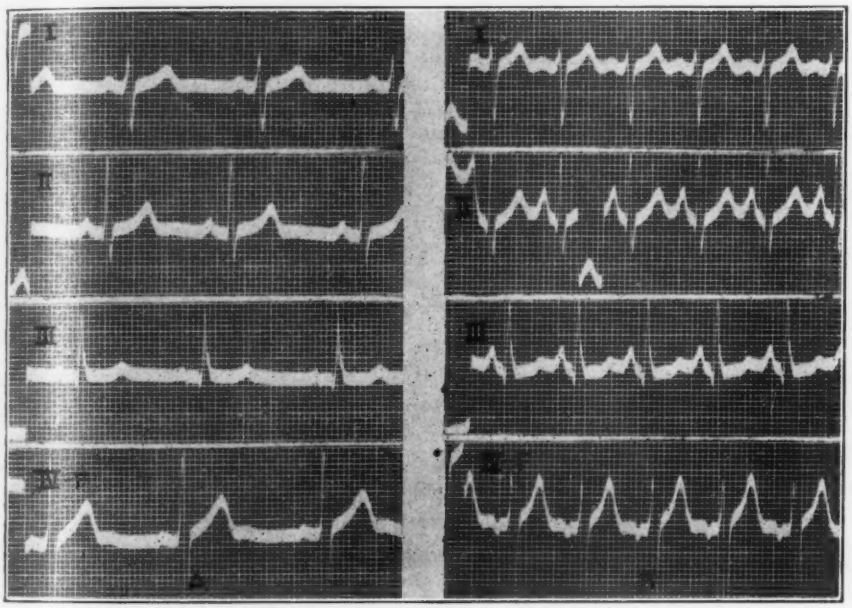

Fig. 7.—Electrocardiograms. *A*, taken at rest before test; *B*, taken at height of urticaria. Note changes in P and T waves. There is also an increase in the deviation of the electrical axis to the right.

On two occasions the use of histamine phosphate and Furmethide together produced a definite urticaria. The same drugs used in a similar manner in a control patient were ineffectual in producing an urticaria.

4. *Electrocardiographic Studies.*—Cardiac disorders, including angina pectoris, tachycardia and ventricular extrasystoles, have been attributed to heat allergy.[5]

5. Duke, W. W.: Relationship of Heat and Effort Sensitiveness and Cold Sensitiveness to Functional Cardiac Disorders Including Angina Pectoris, Tachycardia, and Ventricular Extrasystoles, J. Allergy **4**:38, 1932.

To investigate this problem, electrocardiograms were taken on this patient a number of times and at frequent intervals before exercise, after exercise and after the urticarial eruptions. An electrocardiogram taken before and one taken at the height of the urticaria are shown (fig. 7). A right axis deviation was noted, which seemed to be more pronounced during the urticaria. In addition, there was a sinus tachycardia and the P and T waves seemed to be more pronounced.

In general, one might say that no real significant changes were noted. No arrhythmias or signs of coronary insufficiency were found.

5. *Neuropsychiatric Studies.*—Since there is often a psychogenic element in cases of urticaria, this patient was referred to the psychiatric department of the hospital for a detailed study.[6] An attempt was made to induce urticaria by hypnosis. Narcosynthesis with sodium amytal was also tried. Attempts to reproduce the urticaria by these psychiatric technics were totally unsuccessful. Furthermore, the neuropsychiatric survey failed to reveal any history of neuropathic stigmas, neurotic traits or other emotional or psychologic abnormalities. In fact, the patient was found to have a stolid and placid attitude toward his illness. To quote the psychiatrist, "It is believed that this illness is purely organically conditioned. It is felt that this is one type of somatic illness not amenable to psychotherapy." Finally, a Minnesota psychometric test was performed. The results were entirely within normal limits.

COMMENT

This case presented several interesting phenomena, in addition to being a clinical instance of physical allergy, or more specifically, heat allergy. An attack of urticaria was easily produced experimentally by a fixed form of exercise. Following the urticaria produced by the exercise, a refractory period was found. This refractory period lasted for approximately five hours. Thus, if the patient exercised again an hour or two after the subsidence of the rash a normal response was obtained, that is, no urticaria occurred; and if he exercised again at the end of five hours only a slight urticarial reaction occurred. This refractoriness, or unresponsiveness, as Grant, Pearson and Comeau [2] have preferred to call it, has been observed by others.[7] The mechanism operating in this state of immunity is not clear. Results of our studies with epinephrine and atropine suggest that during the refractory period certain related chemical substances or enzymes are released which bring about a temporary state of refractoriness or unresponsiveness.

This study further demonstrated that exercise was not essential in the production of the urticarial response. Application of external heat

6. Capt. Luis Perelman, Medical Corps, Army of the United States, performed the psychiatric studies.

7. Marchionini, A., and Ottenstein, B.: Schwitzurticaria: Physikalisch-Chemische Untersuchungen zur Pathogenese urticarieller Erkrankungen, Arch. f. Dermat. u. Syph. **163**:61, 1931; cited by Grant, Pearson and Comeau.[2]

brought forth an urticaria in no way different from that produced by exercise. It has been observed by others [8] that the reaction of sensitivity to heat may vary in the type of response and intensity. In some patients the reaction may be chiefly constitutional, and Duke [8a, b] expressed the opinion that in many cases heat prostration and neurocirculatory asthenia are basically problems of sensitivity to heat. Wolkin and his associates [9] have recently studied a group of soldiers training in the desert who were found to be intolerant to excessive heat. In these soldiers there was a failure of the sweating mechanism. These investigators pointed out that this group should be differentiated from those suffering with heat stroke, heat exhaustion and heat cramps. In many patients on exposure to heat less pronounced reactions, such as a thermic headache, erythema or a few hives, are commoner. It is surprising in how many people these milder reactions develop.[8c]

The sensitive response of the gastric mucosa to histamine is a well known fact. The mechanism in cold allergy has been shown [10] to be essentially a release of histamine and has been effectively treated from this standpoint. In cold allergy, the mechanism of which seems in many ways allied to that of heat allergy, Horton, Brown and Roth [10] demonstrated a distinct rise in gastric acidity. In our patient the failure to show any free hydrochloric acid after exercise or after the application of heat would seem to negate the concept that histamine is released in heat allergy. It should be realized, however, that we were dealing with a gastric mucosa rather resistant to stimuli. Ethyl alcohol, a known gastric stimulant, was also unsuccessful. No definite conclusion, therefore, can be drawn from our study on gastric acidity.

During an attack of urticaria there are definite changes in the dynamics of the circulation. Duke [5] observed angina pectoris, tachycardia and cardiac arrhythmias following heat allergy. Depending on the rapidity and degree of exudation of serum into the skin, changes in the volume of blood are to be expected. In addition, there is also evidence of peripheral vasodilatation. The pronounced flushing of our patient was a feature constantly observed. Peripheral vasodilatation is

8. Duke, W. W.: (*a*) Heat and Effort Sensitiveness: Cold Sensitiveness, Arch. Int. Med. **45**:206 (Feb.) 1930; (*b*) Clinical Manifestations of Heat and Effort Sensitiveness and Cold Sensitiveness, J. Allergy **3**:257, 1932. (*c*) Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679 (Nov.) 1938.

9. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert: Thermogenic Anhidrosis, J. A. M. A. **124**:478 (Feb. 19) 1944.

10. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold, J. A. M. A. **107**:1263 (Oct. 17) 1936.

seen with both histamine and acetylcholine. The increase in pulse rate, the drop in blood pressure and the shocklike picture seen at the height of the urticaria in our patient simulated closely the condition observed by Weiss, Robb and Ellis [11] following injections of histamine into human beings. These investigators found that intravenous injections of large doses of histamine phosphate increased the cardiac output, decreased the volume of blood and increased the mean velocity of the flow of blood. These changes were interpreted as being not the result of direct cardiac stimulation but rather a compensatory mechanism to the vasodilatation. That no significant changes were observed electrocardiographically in our patient is understandable when one considers that we were dealing with a young patient with good cardiac reserve. The increase in voltage of the T wave observed at the height of the urticaria may represent the normal condition after exercise.[12] Weiss and his associates [11] commented on the close simulation that exists between the circulatory responses that follow exercise and those that follow injections of histamine.

Studies dealing with urticaria are often complicated by psychogenic factors. The importance of psychic stimuli in producing urticaria has been well established.[13] Gellhorn [14] has recently shown that emotional excitement evokes both adrenergic and cholinergic responses. Partly as a result of Cannon's work [15] most of the attention has been centered on the adrenergic responses. However, during emotional excitement the cholinergic system is also active. Excessive palmar sweating is a striking example of a cholinergic response seen in anxiety states.[16] However, we believe that we have satisfactorily eliminated any criticism that psychogenic factors were important in the genesis of the urticaria seen in our patient.

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11. Weiss, S.; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932.

12. Hartwell, A. S.; Burrett, J. B.; Graybiel, A., and White, P. D.: The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram, with Particular Reference to T Wave Changes, J. Clin. Investigation **21**:409, 1942.

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14. Gellhorn, E.: Autonomic Regulations, New York, Interscience Publishers, Inc., 1943.

15. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton and Company, 1929.

16. Silverman, J. J., and Powell, V. E.: Studies on Palmar Sweating: II. The Significance of Palmar Sweating, Am. J. M. Sc. **208**:297, 1944.

Studies on the patient's sweat mechanism were revealing. Although the patient stated that he thought that he perspired somewhat less than others, at first he appeared to sweat normally while under the heat radiators. However, when he was tested under more controlled experimental conditions, he showed a definitely delayed sweating response over his general body surface. Palmar sweating at all times was found to be perfectly normal. Generalized body sweating differs from palmar sweating on anatomic and physiologic grounds.[16] Generalized body sweating, and not palmar sweating, is concerned with the thermoregulatory mechanism, and it is this type of sweating that was found at fault. Although detailed studies on temperature were not made, the evidence suggests that there was some inherent defect in this patient's thermoregulatory system. Duke [8a, b] attacked the problem from this standpoint and was able to effect cures by improving the thermoregulatory mechanism. Horton [17] also has observed changes in the sweat mechanism of patients with heat allergy and in these patients a diminished sweating response was observed on exposure to heat.

It would seem that in certain patients with a disturbed thermoregulatory mechanism on exposure to heat or following exercise certain chemical substances related to histamine and acetylcholine are released, which set off an urticarial reaction. Evidence for this is shown in the experimental data. Atropine sulfate, a powerful anticholinergic drug, is found to have a definite inhibitory effect on the development of the urticaria. The greater the dose of the drug the less was the urticarial response, and the more delayed was it in developing. Epinephrine, the antagonist of histamine, injected before and during exercise prevented the urticaria and pruritus from developing. Although pilocarpine and choline derivatives have been successfully employed in producing an urticaria,[18] neither Furmethide nor pilocarpine hydrochloride in the doses given was successful in producing an urticaria in our patient when given alone. Similarly, histamine phosphate, whether injected intravenously or subcutaneously, by itself produced no urticaria. However, it is only fair to mention that the drug given intravenously prior to exercise appeared to have a slight inhibitory effect on the production of the urticaria. But when histamine phosphate and Furmethide, a choline derivative, were injected together, a definite urticaria was obtained each time this combination was used. In a normal control these two drugs combined produced no urticaria.

17. Horton, B. T.: Personal communication to the authors.

18. Grant, Pearson and Comeau.[2] Hopkins, Kesten and Hazel.[8c] Marchionini and Ottenstein.[7]

It, therefore, seems likely to us that both histamine and acetylcholine-like substances play a role in the physiochemical background underlying the type of heat allergy seen in this patient. This hypothesis, first proposed by Grant and his co-workers,[2] does not seem unreasonable when one considers that histamine is a normal constituent of the cells of the body and acetylcholine is always released during stimulation of an efferent nerve. Dale, Feldberg and Vogt[19] in 1936 showed that acetylcholine was released at the motor nerve end plates associated with voluntary striated muscle. The release of both histamine and acetylcholine in the body is probably going on all the time but is kept under control by neutralizing enzymes. It is conceivable that in our patient these enzymes, histaminase and cholinesterase, were present in insufficient amounts. In a patient with an inherent defect of the thermoregulatory system, it is possible that on exposure to sufficient heat or exercise more than the usual amount of acetylcholine is released to bring about sufficient sweating. Sweating is the main mechanism by which the body is cooled. The body may overcompensate, so to speak, as it so often does, to attempt to correct a defect. At the same time histamine is also released, and the two substances together bring about an urticarial response in a fashion similar to that produced experimentally. Figure 1 shows graphically the concept of the probable relationship of the various factors operating in the urticarial response in our patient.

It was not possible to carry out a satisfactory therapeutic program, as our patient was discharged from the army. On the basis of our studies, however, possibilities in the way of therapy should be considered. While desensitization with histamine or with acetylcholine is the logical form of treatment, it appears to us that the combined use of the two drugs would provide a still better method of treatment. Other avenues of approach, dealing particularly with the heat-regulatory mechanism, should be mentioned. Thyroid extract elevates the basal metabolic rate and has been used successfully in this condition.[8a] Also injections of foreign proteins, such as typhoid-paratyphoid combined vaccine, characteristically affect the thermoregulatory mechanism and might be tried. That a state of unresponsiveness can be induced is indicated by our studies dealing with the refractory period found after repeated exercise. Desensitization, therefore, should be considered in the form of a program of graduated exercise or of increased exposure to moist or dry heat in a manner similar to the desensitization for cold allergy.

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19. Dale, H. H.; Feldberg, W., and Vogt, M.: Release of Acetylcholine at Voluntary Motor Nerve Endings, J. Physiol. **86**:353, 1936.

SUMMARY AND CONCLUSIONS

The case of a patient with a physical allergy (heat and exercise) is presented.

The mechanism in this type of allergy can be demonstrated better on the basis of both histamine and acetylcholine than on the basis of one chemical substance alone.

Desensitization with both histamine and acetylcholine is proposed as a method of treatment.

CHRONIC HEMOLYTIC ANEMIA

Observations on the Effect of Fat Content of the Diet and Multiple Red Cell Transfusions

ROBERT S. EVANS, M.D.
SAN FRANCISCO

A COMPREHENSIVE review of the present knowledge concerning the hemolytic disorders has recently been presented by Davis.[1] While many acute and chronic forms of hemolytic anemia can now be recognized as disease entities, in a large proportion of the cases observed here in recent years no familial factor, etiologic agent or hemolytic system could be demonstrated. This group of cases has usually been described under the heading of acquired hemolytic anemia. Dameshek and Schwartz [2] have emphasized the acute and subacute course of the disease but have recognized more chronic forms. These authors were able to demonstrate isohemolysins in the blood of 3 patients,[3] but the presence of such substances in the circulation, as determined by tests in vitro, must be a rare occurrence.[4] Autohemolysins have not been demonstrated, though autoagglutinins active at body temperature have been reported.[5]

Further study of patients with acquired hemolytic anemia is particularly important because of the unpredictable response to splenectomy that has been observed in this group. While some observers have reported a high percentage of good results, others have had less success. At the present time there are no criteria for predicting whether this major operation will be successful or futile in the individual case.

Miss Rose Duane assisted with the hematologic procedures.

From the Department of Medicine, Stanford University School of Medicine, San Francisco 15, Calif.

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2. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia, Medicine **19**:231 (May) 1940.

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4. Mason, V. R.: Acquired Hemolytic Anemia, Arch. Int. Med. **72**:471 (Oct.) 1943.

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During the past several years my colleagues and I have had the opportunity to follow the course of 2 patients whose hemolytic anemia has been chronic and fairly severe. Both patients have undergone splenectomy with some evidence of benefit, but the anemia, along with signs of increased destruction and formation of blood, has persisted. In spite of similarities in the course of the disease one difference which seems of fundamental importance has always been present. The erythrocytes of one patient have always shown spherocytosis and increased fragility in hypotonic saline solution, while the erythrocytes of the other have persistently exhibited a normal resistance to hemolysis in hypotonic saline solution and an absence of spherocytosis. Studies of the rate of destruction and formation of erythrocytes were undertaken in the hope of demonstrating further fundamental differences between these patients.

Johnson and his colleagues [6] have recently called attention to the importance of lipemia in destruction of erythrocytes, and previous measurements [7] have shown that the output of urobilinogen of human infants is increased with a diet high in fat content. It seemed possible that in the presence of accelerated destruction of red cells the fat content of the diet played an important role in the rate of hemolysis in 1 or both patients. We have attempted, therefore, to determine what effect, if any, diets of high and low fat content would have on the rate of destruction of red cells.

The introduction of normal erythrocytes into the circulation of persons with hemolytic anemia by transfusion also has aspects of theoretic and practical interest. If the survival time of transfused erythrocytes is shown to be normal, it would imply that the increased destruction of the native erythrocytes was produced by selective autohemolytic substance, which seems unlikely, or that a defect in cell structure exists which predisposes to a shorter life span. Interesting observations of this nature have been made by Dacie and Mollison,[8] which indicate that transfused cells have a normal longevity in familial hemolytic jaundice and a reduced survival time in acquired hemolytic anemia.

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7. Josephs, H. W.; Holt, L. E.; Tidwell, H. C., and Kajdi, C.: The Influence of Dietary Fat upon the Excretion of Urobilin, Bull. Johns Hopkins Hosp. **71:**84 (Aug.) 1942.

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The recent use of multiple transfusions of concentrated red cells has permitted the restoration of the circulating hemoglobin to normal levels in a short space of time. The elimination of the anemic state in a patient with hemolytic anemia should have a profound effect by diminishing the rapid formation of blood to a normal range and consequently by modifying one of the constant features of the disease. In our patients, therefore, we have tried to gain indirect evidence as to the fate of transfused normal cells and to measure the rate of destruction and formation of blood following the restoration of the circulating hemoglobin to normal by transfusions of red cells.

METHODS

All hematologic determinations were done with venous blood. The mixture of ammonium oxalate and potassium oxalate described by Heller and Paul [9] was used as the anticoagulant. Determinations of hematocrit values were done by the Wintrobe [10] method. Preparations for counting reticulocytes were made with the coverslip technic, using a thin dry film of cresyl blue as the vital stain. The quantitative studies of fragility of erythrocytes in hypotonic saline solutions were done by the method of Waugh and Asherman.[11] Determinations of bilirubin in the blood were made by the method of Malloy and Evelyn.[12] The method described by Watson [13] was used in following the output of fecal urobilinogen in one patient. The other patient had an ileostomy opening, so that some trial and error were necessary before a satisfactory method of quantitating the excretion of pyrrole pigment was found. The Watson method of extraction showed that output of urobilinogen was only 10 to 15 mg. per day. Aqueous and alcoholic extracts of the excreta through the iliostomy opening gave strong color reactions with the diazo reagent, but the results were variable. However, the method of Malloy and Evelyn,[14] in which the bilirubin in a dilute sample is oxidized to biliverdin with a hydrogen peroxide reagent and the amount determined colorimetrically, yielded reproducible results and was used as follows: A two or three day collection of excreta from the artificial anus was diluted to 4,000 cc. with water and stirred with an electrically driven propeller to insure thorough mixing. A 200 cc. sample was diluted to 4,000 cc. and stirred thoroughly with the same apparatus. To

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10 cc. of the dilute material 25 cc. of the hydrogen peroxide reagent and 15 cc. of 95 per cent alcohol were added. The yellow color of the solution turned to a bright greenish blue and was maximum at one hour. A sample was centrifuged, and the amount of biliverdin in the supernatant fluid was read directly in the colorimeter. The amount of pigment remaining in the small amount of sediment was found to be negligible.

REPORT OF CASES

CASE 1.—H. S. a 38 year old woman of Greek birth had undergone a colectomy for ulcerative colitis and a splenectomy for hemolytic anemia, which had continued as a chronic process. She entered the United States in 1932 and had lived in San Francisco since. Pregnancies in 1933 and 1935 were uneventful, and both children are living and well.

There is no history of illness until March 1937, when cramping abdominal pains, accompanied with diarrhea with pus and blood in the stools, began. After several months without improvement an ileostomy was done, but she continued to have an active rectal discharge. In July 1939 she was admitted to the San Francisco Hospital because of pain, swelling and tenderness in several joints. Observations relative to the joints were consistent with rheumatoid arthritis. There was an abscess about the artificial anus, and roentgenograms of the colon showed a tubular appearance with loss of haustrations. During the ensuing year a three stage colectomy was done. Pathologic examination of the specimens confirmed the diagnosis of idiopathic chronic ulcerative colitis with polypoid degeneration. No disease was demonstrated in the ileum. Her postoperative periods were complicated by parotitis and cystitis, but she gained weight and strength, and her symptoms referable to the joints subsided. She was discharged in July 1940.

An anemia which she exhibited on entry responded to iron therapy and the removal of her infected colon. There were no signs of increased hemolysis throughout her prolonged stay at the hospital.

She was next seen in the outpatient clinic of Stanford-Lane Hospital, in October 1940, because of a recurrence of her arthritis. A course of gold therapy was instituted, and injections of a 0.01 per cent solution of colloidal gold were given as illustrated in chart 1. There were no immediate reactions to the injections, but during the latter half of the course of therapy she complained of having mild abdominal pain and discomfort at intervals between injections. The leukocyte counts during the course of gold therapy showed no significant change, but the steady fall in hemoglobin is evident. As the anemia developed polychromatophilic staining of a large percentage of erythrocytes was noted in the blood smears.

Six months after cessation of gold therapy her anemia failed to improve, and she was admitted to the San Francisco Hospital, where icterus, anemia and splenomegaly were noted on admission. Reticulocytes were found to be 16 per cent of all red blood cells, and the icterus index was 20. Sternal biopsy showed normoblastic hyperplasia. During the next three months her hemoglobin continued to fall, and there was no sustained response to transfusions. Her erythrocytes showed some increased susceptibility to hemolysis in hypotonic saline solution.

Splenectomy was performed Feb. 5, 1942. The spleen weighed 450 Gm. and exhibited a thickened capsule and a soft engorged parenchyma. The spleen pulp was engorged with erythrocytes, and phagocytic endothelial cells were full of brown pigment granules. The malpighian bodies were small, and subcapsular hemorrhages were noted. The postoperative course was uneventful; her hemoglobin rose spontaneously from 38 per cent to 69 per cent of normal during the first few weeks after splenectomy, and she was discharged as improved. This period of partial remission was followed by a drop in hemoglobin to a level of 40 per cent to 50

per cent of normal, where it remained on all observations for a period of two years, except for a brief rise following transfusions. Signs of increased destruction and formation of blood have been present constantly. Reticulocyte counts have varied from 20 to 32 per cent, and nucleated, red blood cells have been noted in all blood smears. She has exhibited a constant mild icterus, and the icterus index has varied from 20 to 40. She has had mild exacerbation of symptoms referable to the joints from time to time since splenectomy, but during the last nine months her arthritis has been quiescent. She has remained ambulatory since splenectomy and able to do light housework. Her complaints of easy fatigue, weakness and dizzy sensations have been present most of the time.

Physical Examination.—At the beginning of the experimental period, on Aug. 25, 1944, some thirty months after splenectomy, her weight was 44.8 Kg. She

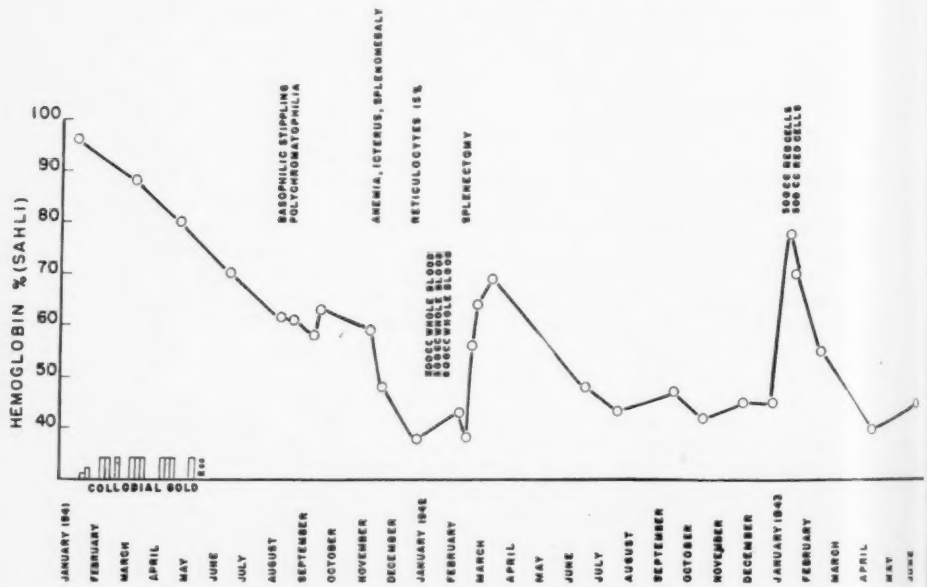

Chart 1 (case 1).—There is a steady drop in hemoglobin during and following injections of a 0.01 per cent solution of colloidal gold. Note the temporary spontaneous rise following splenectomy and the temporary rise following transfusions (two transfusions of 500 cc. of whole blood and one of 300 cc. on one occasion, and two transfusions of 500 cc. of red blood cells on another).

appeared to be about her stated age. The skin had a yellow tint, and the mucous membranes and palms were pale. There were no deformities of skull or spine. The scleras were icteric, and pupillary reactions to light and accommodation were normal. The tongue was normal. The teeth were in good repair with amalgam fillings. Tonsils were present but not remarkable. There was no general adenopathy. The thyroid isthmus was palpable but not enlarged, and the breasts were normal. The chest was clear to percussion and auscultation. The heart was not enlarged to percussion, and the rhythm was regular. There was a blowing systolic murmur along the left sternal border. The blood pressure was 85 mm. of mercury

systolic and 50 diastolic. Abdominal examination showed an ileostomy opening on the right and the colectomy and splenectomy scars. The edge of the liver could be felt at the costal margin. Previous pelvic examinations had revealed nothing abnormal. The extremities and joints were normal except for slight swelling and tenderness of the right knee joint.

Laboratory Data.—Examination of the blood at the beginning of the experimental period showed the following values: hematocrit value, 27; hemoglobin, 57 per cent Sahli (9.8 Gm. per hundred cubic centimeters of blood); erythrocytes, 2,750,000 per cubic millimeter; mean cell volume, 99 microns; mean cell hemoglobin, 35 micromicrograms; mean cell hemoglobin concentration, 36 per cent; reticulocytes, 14.5 per cent of all red blood cells, and leukocytes, 14,200 per cubic millimeter. The differential count of the leukocytes was not remarkable—57 per cent neutrophils, with 5 per cent banded forms; eosinophils, 3 per cent; monocytes, 4 per cent, and lymphocytes, 36 per cent. One per cent of nucleated cells were normoblasts. In the blood smear the erythrocytes varied greatly in size, and the most predominant cell was of smaller diameter than normal and densely stained. The other prominent cell type was of much greater diameter and usually showed polychromatophilic staining. A Price-Jones curve illustrated this great variation in cell diameter. The average cell diameter was 6.66 microns, and the average cell thickness was 3.9 microns. Susceptibility to hemolysis in hypotonic saline solution was greatly increased, as shown in chart 3. Hemolysis of the patient's cells was complete before hemolysis of normal cells began.

Her blood was of group O and was Rh positive.

The specific gravity of specimens of urine varied between 1.006 and 1.025. All specimens have shown negative reactions to tests for sugar, protein and bile. No abnormalities have appeared in the sediment. A twenty-four hour collection of urine extracted by the Watson method showed an absence of urobilinogen from the urine, a finding consistent with the small amount of urobilinogen present in the material collected from the artificial anus.

The material from the artificial anus was semisolid and weighed about 600 Gm. daily. The color varied from green to brown. No gross change in character or amount of material from the antificial anus occurred when the fat content of the diet was changed.

Experimental Data.—Effect of Diets Low and High in Fat: The diet history showed that she had been taking a diet relatively low in fat; hence observations were begun after a period in which the fat content and caloric intake were regulated. The data accumulated during the periods of low and of high intake of fat are presented in chart 2. As can be seen, no significant variation in hematocrit level or percentage of reticulocytes occurred. There is, however, suggestive evidence of increase in pyrrole pigment metabolism during the period of high intake of fat. The excretion of bilirubin, which averaged 680 mg. per day during the period of low intake of fat, was 780 mg. per day during the period when a diet high in fat was given. The level of bilirubin in the blood was also somewhat higher during the period in which the intake of fat was high. These differences are not significant, however, in view of the increased output of pigment demonstrated in a later control period when she was taking a diet low in fat content. At the termination of these observations a transfusion of 250 cc. of red cells was given to determine whether an increase in output of bilirubin would occur which could be measured by the method used. The excretion of 1,200 mg. per day following this transfusion is probably significant, since it is over 200 mg. higher than any previous determination.

Effect of Transfusions of Red Cells: Following an interval of fifty-two days, during which time she returned to a diet low in fat, observations as to the effect of transfusion of large amounts of red cells were begun. The data as to hematocrit level, percentage of reticulocytes and output of bilirubin in the excreta from the artificial anus are presented in chart 2.

The control period indicates that the hemolytic process was going on at a higher rate than previously. The hematocrit was at a lower level, the percentage of reticulocytes was almost twice the previous level, and the output of pigment increased to 1,000 mg. daily or more. The level of bilirubin in the blood was

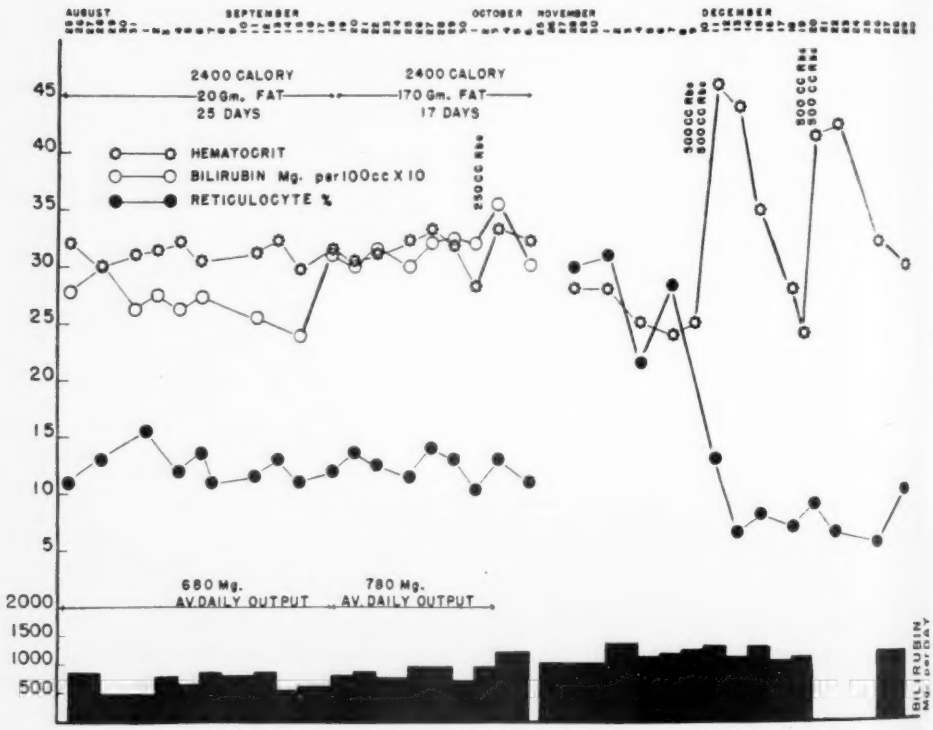

Chart 2.—Output of bilirubin in the excreta through the artificial anus from the patient with spherocytosis during periods of low and high intake of fat and following multiple transfusions of red blood cells.

also higher during this period, with levels of 5.5 mg. per hundred cubic centimeters on December 7 and 9. However, she exhibited no particular increase in symptoms as a result of the increased destruction of blood.

She was given transfusions of 500 cc. of concentrated red blood cells on two successive days without reaction. The hematocrit level was 45 the day following the second procedure. Two days after the second transfusion the curve of fragility in hypotonic saline solution was again determined and found to be nearly identical

with the curve before transfusion, even though the hematocrit level remained at 45, indicating that nearly one half the erythrocytes present were the transfused cells. There was a rapid fall in the hematocrit level following this observation, and at the end of seven days it had returned to 25, the level before transfusion. She was again given the same amount of blood in two successive procedures, and a sample of blood was taken immediately after completion of the second transfusion. Fragility curves as illustrated in chart 3 indicate a distinct shift toward normal, with 25 per cent of the hemoglobin liberated within the same range of hypotonicity in which normal cells are hemolyzed. Two days later there was a shift of the curve back to the type before transfusion, without a fall in the hematocrit value.

These observations were repeated again at a later date not shown on the chart, when a single transfusion of 600 cc. of red cells was given. There was the same shift toward normal immediately following transfusion, but observations at the end of twenty-four hours showed that the increase in fragility of the transfused

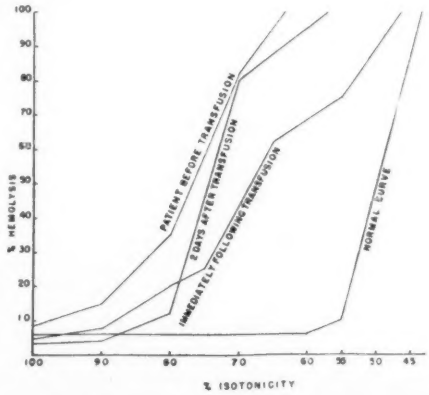

Chart 3.—Quantitative fragility curves made before, immediately after and two days following multiple transfusions of red blood cells given to the patient with spherocytosis. Immediately after transfusion 25 per cent of the red blood cells are hemolyzed within the range of hypotonicity within which normal cells are hemolyzed. A distinct shift toward the curve before transfusion occurs thereafter.

cells was largely complete in this time. Blood smears made immediately following transfusions showed a large percentage of cells with normal diameter and pale centers, while those made twenty-four and forty-eight hours later showed few if any normal-appearing mature erythrocytes in that all were lacking the pale central area. The average diameter of the nonreticulated cells was 7.7 microns following transfusion, while twenty-four hours later it was found to be 6.6 microns. The hematocrit value immediately after the transfusion was 40, and the erythrocyte counts averaged 4,460,000 per cubic millimeter. The mean corpuscular volume was therefore 90 cubic microns. In twenty-four hours the erythrocyte counts had dropped to 3,600,000 per cubic millimeter, while the hematocrit value was 38.5. According to these determinations the mean corpuscular volume had increased to 107 cubic microns. During the same twenty-four hour period the hemoglobin dropped from 13.25 to 11.9 Gm. per hundred cubic centimeters of blood.

The increase in mean cell volume accompanied by a diminished cell diameter indicates an increase in mean cell thickness or tendency toward spherocytosis. This change in cell structure was reflected in the curves of fragility in hypotonic saline solution, which are almost identical with those presented in chart 3. The close relationship between increased susceptibility to hemolysis in hypotonic saline solutions and increased cell thickness has been amply demonstrated.[15]

Attempts made to duplicate this phenomenon in vitro were not successful. Washed cells of type O from a normal person were mixed with normal serum of type O and serum from the patient in 20 per cent suspensions. Samples of these suspensions were allowed to stand at 37 C., at room temperature and at refrigerator temperature. A fourth pair was kept in constant agitation at room temperature. Fragility studies done at two day intervals showed a parallel development of increased fragility in hypotonic saline solution of the cells suspended in the patient's serum and in the control serum in all 4 instances.

These studies were repeated three times at various intervals up to thirty days following transfusion, but continued to give negative results. The addition of 0.5 cc. of guinea pig serum to each 2 cc. of cell suspension had no measurable effect.

The rapid drop in hematocrit value following the transfusions shown in chart 2 was not accompanied with clinical symptoms. Hemoglobinemia aud hemoglobinuria did not appear, and there was little if any elevation of the icterus index, which varied between 40 and 50 before and after transfusions. As shown by chart 2, there was no increase in output of bilirubin following the rapid fall in the hematocrit value. This was difficult to explain in view of the massive hemolysis which must have taken place. It may be that 1,300 to 1,400 mg. per day represents the maximum possible rate of production of bilirubin in this person.

CASE 2.—D. T., a 51 year old man of Italian extraction, was first seen in this clinic in 1933 because of blood-tinged sputum, which appeared during an attack of bronchitis. A roentgenologic examination of the chest, an examination of the sputum and a Wassermann test of the blood revealed nothing abnormal.

Five years later, in February 1939, he reappeared, complaining of shortness of breath of three months' duration. He felt that he had been losing strength for at least a year. He had not noted jaundice at any time, but the skin and scleras were found to be icteric. Dilated vessels of the face gave a ruddy appearance, but the mucous membranes and nail beds showed pronounced pallor. He was urged to enter the hospital, and finally did so three months later. Little further could be added to the history of his present illness. His dyspnea, pallor and jaundice had apparently been very insidious in onset and not accompanied by abdominal pain or change in the color of the urine.

He was born in Italy but had lived in San Francisco from the age of 2. No childhood diseases were recalled. Infections of the upper respiratory tract accompanied with bronchitis had been frequent during his adult life. He contracted a type of urethritis in 1933 which was said to be gonorrheal. Nocturia had been present for several years. Hernioplasties were done in 1912 and 1918. His consumption of alcohol had been moderate and consistent but had never interfered with good habits of eating. His father had died of cancer. There was no history of jaundice or anemia in parents or siblings.

Physical Examination.—Aside from the pallor of mucous membranes and nail beds and the icterus, the physical abnormalities observed were incidental. The

15. Castle, W. B., and Daland, G. A.: Susceptibility of Mammalian Erythrocytes to Hemolysis with Hypotonic Solutions, Arch. Int. Med. **60**:949 (Dec.) 1937.

skin showed no nevus araneus. The pupils were equal and reacted well to light and to the necessity for accommodation. Pyorrhea was present about carious teeth. Cervical and generalized adenopathy was absent. There were a few scattered wheezes and rhonchi heard over the chest. Cardiac enlargement was questionable. The rhythm was regular, and a soft systolic murmur was heard over the precordium. The blood pressure was 130 mm. of mercury systolic and 60 diastolic. The abdomen was obese, and the edge of the liver was felt below the costal margin, but the spleen was not palpable. No other masses were felt. There was a hydrocele on the left. The prostate was enlarged symmetrically and was moderately firm. The extremities were free of edema, and the deep tendon reflexes were equal and active. Position and vibratory sense were normal.

Laboratory Examination.—Examination of the blood gave the following values: hematocrit value, 13; erythrocytes, 1,090,000 per cubic millimeter; hemoglobin, 26 per cent Sahli (4.47 Gm. per hundred cubic centimeters); mean cell volume, 119 cubic microns; mean cell hemoglobin, 41 micromicrograms, and mean cell hemoglobin concentration, 34 per cent. Reticulocytes were 17 per cent, and there were about 250 normoblasts per cubic millimeter. The leukocyte count was 6,200, of which 76 per cent were polymorphonuclear leukocytes, 14 per cent lymphocytes and 10 per cent monocytes. Platelets numbered 250,000 per cubic millimeter. All specimens of serum examined were reported to show a slight hemoglobinemia, and the reaction to the direct Van den Bergh test was negative, to the indirect, 1.44 units. There was no increase in susceptibility of the red cells to hemolysis in hypotonic saline solution. The Donath-Landsteiner phenomenon could not be demonstrated, and tests for acid hemolysins were negative at this and at subsequent dates. Several preparations failed to demonstrate sickling.

His blood was found to be of group OMNRh +.

A biopsy of the bone marrow showed normoblastic hyperplasia.

Specimens of urine were of normal color and gave negative reactions to tests for protein and sugar, and the urine sediment contained nothing of significance. Stool specimens were free of gross and occult blood.

A determination of urea in the blood showed 45 mg. of urea per hundred cubic centimeters, and the total proteins in the blood were 6 Gm. per hundred cubic centimeters. Gastric analysis showed no free hydrochloric acid after the administration of histamine. Roentgenograms of the chest showed nothing abnormal.

Course.—There was little change during his stay of six weeks in the hospital. He remained afebrile and felt well while at rest. Hepatic extract given intramuscularly failed to increase reticulosis or to affect the hemoglobin level. There was no decrease in the signs of rapid destruction and regeneration of blood. He refused splenectomy and before discharge was given one transfusion of whole blood which produced a temporary rise in hemoglobin level.

During the next two years he was seen from time to time without change in blood values or in his symptoms and signs of his severe chronic hemolytic anemia.

Second Admission.—July 10, 1942: He was readmitted because of extreme dyspnea. The hemoglobin value was 21 per cent (3.6 Gm. per hundred cubic centimeters); there were 990,000 erythrocytes per cubic millimeter, and reticulocytes comprised 10 per cent of the red blood cells. Leukocyte counts were within normal range. On this admission the edge of the spleen was felt 2 cm. below the costal margin. There was definite cardiac enlargement. Two transfusions of whole blood raised the hemoglobin level to 38 per cent before the patient's discharge.

Third Admission.—Oct. 10, 1942: He was readmitted with a hemoglobin value of 26 per cent. Five transfusions of whole blood brought the hemoglobin level to 64 per cent, and he was discharged.

Fourth Admission.—March 17, 1943: This admission followed an attack of abdominal discomfort and an increase in icterus. He was afebrile, and leukocyte counts were normal. The spleen was felt as before. The hemoglobin value was 22 per cent, and the reaction to the indirect van den Bergh test was 7.4 units. He was again given a transfusion and discharged from the hospital.

	Peripheral Vein	Splenic Vein
Hematocrit value	46	44
Hemoglobin	82 per cent	80 per cent
Erythrocytes	4,400 per cubic millimeter	4,100 per cubic millimeter
Reticulocytes	3.6 per cent	3.8 per cent
Leukocytes	13,100	13,000
Platelets	169,300	166,800
Plasma	Hemoglobinemia +	Hemoglobinemia +
Mean corpuscular volume	104 cubic microns	107 cubic microns
Mean corpuscular diameter	8.86 microns	7.96 microns
Mean corpuscular thickness	1.8 microns	2.1 microns

Fragility in Hypotonic Saline Solution

	Hemolysis Begun	Hemolysis Definite	Hemolysis Intense	Hemolysis Complete
Blood from peripheral vein	0.50	0.42	0.38	0.28
Blood from splenic vein	0.54	0.46	0.40	0.30

Fifth Admission.—April 29, 1943: The hemoglobin level was 36 per cent, and the hematocrit value was 19. He was given two transfusions, totaling 500 cc. of concentrated red cells, without reaction, and the hematocrit value was raised to 25.

Sixth Admission.—May 19, 1943: His hematocrit value had dropped from 25 to 21 in nineteen days. After one transfusion of 500 cc. of concentrated cells he was discharged.

Seventh Admission.—July 27, 1943: During three weeks before admission he had become increasingly short of breath. He was icteric as usual, and the spleen and liver were palpable as before. The hematocrit value was 14, and the hemoglobin was 29 per cent. He was given 1,500 cc. of concentrated red cells in three procedures without reaction, which raised the hematocrit value to 36 and the hemoglobin to 78 per cent. The dyspnea was relieved.

Eighth Admission.—Oct. 6, 1943: The hematocrit value had fallen from 36 to 16 in two months' time, and his symptoms of severe anemia had returned. He at last consented to splenectomy, and, following repeated transfusions of concentrated red cells, splenectomy was performed on Oct. 9, 1943. During the procedure a sample of blood was withdrawn from the splenic vein. The results of examination of this sample are compared with those made on a sample taken from the antecubital vein at the same time.

His postoperative course was uneventful, and his icterus diminished gradually. He was discharged fifteen days after operation, only to be readmitted seven days later.

Ninth Admission.—Oct. 31, 1943: Three hours before admission he noted weakness of the right arm and leg and inability to coordinate his speech. There were definite motor weakness on the right and a mild degree of aphasia. His blood picture had changed very little, although the icterus index was still 15. Counts of blood platelets were 290,000 and 313,000 per cubic millimeter. He improved rapidly and was discharged at the end of nine days.

During the ensuing months he was seen from time to time. There was a gradual fall in the hematocrit level at the rate of 1 to 1.5 mm. per month, and the icterus of the plasma became more pronounced.

On Oct. 5, 1944, a diet survey showed that he was consuming a diet high in fat, so that observations were begun while he was ambulatory after regulating his diet as to caloric intake and fat content. Results of these observations are presented in chart 4.

Tenth Admission.—Oct. 22, 1944: One year following splenectomy, when he was admitted for further observation, blood values were as follows: hematocrit value, 21.5; hemoglobin, 38 per cent (6.5 Gm. per hundred cubic centimeters),

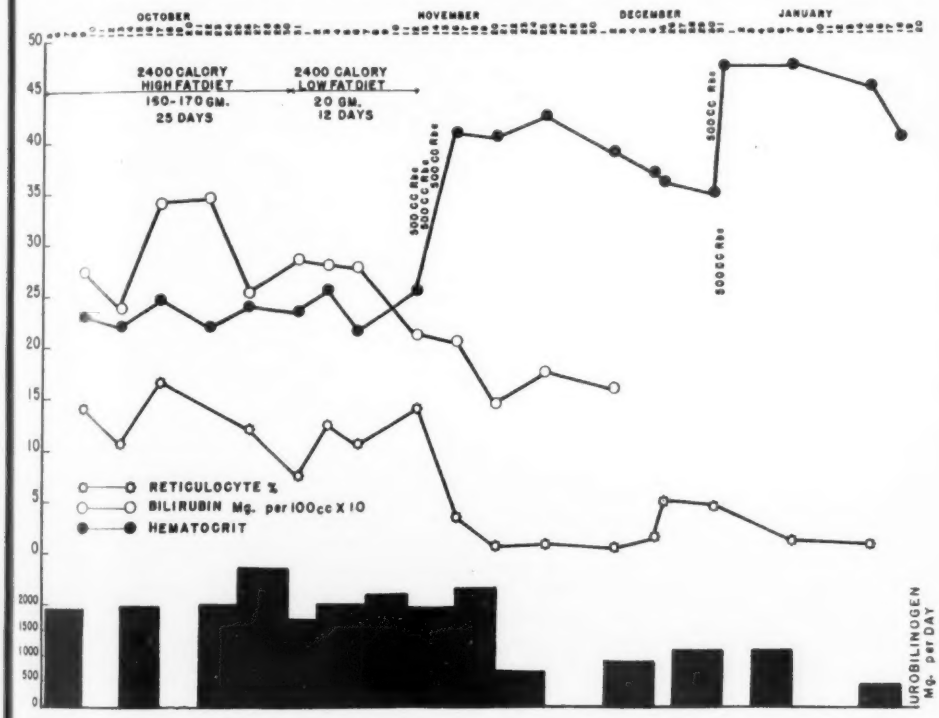

Chart 4.—Determinations of output of fecal urobilinogen of the patient who exhibited normal fragility of red blood cells in hypotonic saline solution and "pseudomacrocytosis" during periods of high and low intake of fat and following multiple transfusions.

and erythrocytes, 1,780,000 per cubic millimeter, with 30 per cent reticulocytes. Examination of the blood smear showed cells of normal and of greater than normal diameter exhibiting a normal pale center area. Few, if any, small densely staining cells lacking the pale central area were seen. The absence of spherocytes is evident from the Price-Jones curves, several of which fail to show any red blood cells of less than the normal range of diameter. The icterus index was 50, and the serum bilirubin was 3.4 mg. per hundred cubic centimeter. The leukocyte count was within normal range.

All his former symptoms of weakness and dyspnea on slight exertion had reappeared. No new physical abnormalities were evident. The blood pressure was 132 mm. of mercury systolic and 65 diastolic.

Course: He was continued on a diet high in fat for a period of nine days, making a total of twenty-four days, and then was given a diet low in fat for twelve days. Following this, 1,500 cc. of fresh concentrated red cells were given in three procedures, which raised the hematocrit value to 41, and he was discharged feeling greatly improved. He was able to return to work and was free of major symptoms for a period of forty-five days, when he was readmitted because of slight weakness; he felt that he would soon be incapacitated for moderately hard physical work.

Eleventh Admission.—Dec. 13, 1944: He was given 1,000 cc. of concentrated red cells in two procedures without reaction. The hematocrit value was raised from 35 to 48. He was discharged the day following entry feeling well and returned to work for six days. Then there developed an infection in the upper respiratory tract, for which he was seen and told to remain at home and in bed.

Twelfth Admission.—Jan. 18, 1945: On this date he experienced the onset of weakness of the right arm and inability to speak coherently. Physical examination showed weakness of the right hand and arm and motor aphasia. During the next few days the aphasia became complete, and he became weak and finally paralysis of the whole right side, including the face, set in. His temperature became elevated, and he sank into coma and died on the sixth day in the hospital.

Pathologic Examination: Spleen. The spleen weighed 400 Gm. The cut surface was smooth and firm, and there were no infarcts. The splenic pulp was congested and contained large numbers of reticuloendothelial cells, erythrocytes, macrophages and neutrophilic leukocytes. The reticuloendothelial cells contained phagocytized erythrocytes and hemosiderin granules.

Autopsy: The heart weighed 400 Gm., and none of the chambers was dilated. The coronary arteries were patent. There were red patches of consolidation in the lower lobe of the right lung. The peribronchial lymph nodes were not enlarged. No accessory spleen could be found. The liver weighed 2,200 Gm. and exhibited a smooth surface. A tiny fresh thrombus was found in one of the hepatic veins. The bile ducts and gallbladder were normal. Examination of the brain showed a small thrombus in the sagittal sinus. The entire left half of the cerebrum was soft and easily torn. The cerebral arteries were normal except for the left middle cerebral artery, which was distended by a reddish gray thrombus.

Microscopic examination showed slight intimal thickening of the left middle cerebral artery and no inflammation of the vessel around the fresh cellular thrombus. There was complete fresh necrosis of the left corpus striatum. The liver showed moderate atrophy of the central cells and dilatation of the sinusoids. Occasional tiny areas of focal necrosis were noted. Many of the small efferent veins contained fresh thrombi. There was little hemosiderin in the Kupffer cells. The kidney presented an unusual picture with large amounts of hemosiderin in the tubular epithelium. The epithelial cells were otherwise normal. The femoral marrow was hyperplastic, and phagocytosis of red cells was noted. There were large amounts of blood inside and outside the sinusoids, and leukoblastic elements were inconspicuous.

Experimental Data.—The Effects of High and Low Fat Diets: As stated previously, this patient had been consuming a diet which contained approximately 160 Gm. of fat daily. Observations which were begun while he continued with this regular diet at home are presented in chart 4. The diet high in fat was continued for eight days after he was admitted to the hospital, and he was then

changed to a diet low in fat, which was continued for twelve days. As can be seen from the chart, no significant change occurred in the hematocrit level, the reticulocyte count, the bilirubin in the blood or the output of urobilinogen in the feces during the course of the low fat intake. Perhaps twelve days is not sufficient time to give a conclusive answer, particularly in view of the somewhat lowered level of bilirubin in the blood at the termination of the observations, but it was not possible to extend the period of observation. He was therefore returned to a regular diet, and multiple transfusions were begun.

The Effect of Red Cell Transfusions: He was given transfusions of 500 cc. of concentrated red cells on three successive days, which raised the hematocrit level from 24 to 41 and the hemoglobin to 13 Gm. per hundred cubic centimeters. The percentage of reticulocytes fell to a normal range following the pronounced increase in the circulating hemoglobin. The bilirubin in the blood remained at a lower level after transfusions. The sudden decrease in daily output of urobilinogen in the stool is shown by the measurements made beginning five days following the last transfusion. The output of urobilinogen, which had been 2,000 mg. daily or higher, suddenly fell to 700 mg. per day. During the next forty-five days the hemotocrit value fell slowly to a level of 35, the percentage of reticulocytes remained at the level of 1 or 2 for most of that time, and the excretion of urobilinogen, while considerably above normal, was roughly half the previous amount.

It was intended that the excretion of urobilinogen could be followed as the anemia became more severe and regeneration of blood became more rapid, but the patient felt that he must remain at work; hence he was given two transfusions of concentrated cells, which raised the hematocrit value to 48, in the hope that the formation of blood would be completely inhibited for a time. A determination of urobilinogen excretion begun three days later showed no decrease in output. However, the last determination, completed at the time of onset of the cerebral thrombosis and hemorrhage, showed an excretion of less than 500 mg. daily. Since he was suffering from a respiratory infection at the time and accompanying disturbance of bowel activity, it may be doubted that this was a complete collection, even though the patient insisted that it was.

COMMENT

There can be no doubt that the chronic anemia in both patients was maintained by an accelerated rate of destruction of erythrocytes. Destruction of blood as measured by the excretion of bilirubin and urobilinogen, has been shown to be many times normal. Rapid formation of blood, indicated by 10 to 30 per cent reticulocytes in the circulating blood, has been constantly in evidence throughout several years of observation. The hemolytic anemia developed during adult life in both patients, and in neither case is there evidence in the past history to suggest a previous hemolytic disorder. The patient whose cells exhibit spherocytosis has 2 daughters whose erythocytes show a normal resistance to hemolysis in hypotonic saline solution. In both patients the hemolytic process developed insidiously and was manifested by the gradual development of symptoms referable to the anemia. No change of living habits or state of health preceded the onset of the disease in the man. The other patient was receiving gold therapy for

arthritis at the time that her hemoglobin and erythrocyte count began to fall. Chart 1 shows a steady drop in hemoglobin to the point where jaundice, splenomegaly and reticulosis gave convincing evidence that the anemia was hemolytic in origin. Disorders of hemopoiesis, namely aplastic anemia, granulocytopenia, and thrombopenic purpura, have all been observed after the use of gold therapy,[16] but I have been unable to find a report that hemolytic anemia has resulted from its use. It is difficult to believe, however, that the administration of a gold preparation and the onset of accelerated destruction of the blood were purely coincidental. On the other hand, if gold therapy was instrumental in initiating the process it is not explained why it increased in severity and became chronic long after the injections of the gold preparation were discontinued, since hemolytic anemias due to lytic substances or to hypersensitivity usually subside after the removal of the causative agent.

There is good evidence that the splenectomy had a distinctly beneficial although largely temporary effect for both patients. The first patient had a spontaneous rise in hemoglobin from 38 to 65 per cent during the first few days following splenectomy. However, three months later the hemoglobin was found to be close to the level prevailing before the splenectomy. It could be argued that splenectomy had some lasting benefit, since the anemia was evidently gradually increasing in severity at the time the spleen was removed. There is of course no proof that it had not reached its lowest point and become stabilized just prior to splenectomy. The second patient underwent splenectomy after the hematocrit value had been restored to normal by transfusions of red cells. However, the rate of fall of the hematocrit value following splenectomy was much slower than it had been following previous transfusions of red cells. Prior to the splenectomy the hematocrit level had dropped from a normal range to the level before transfusion within two months' time. Following splenectomy the fall was so gradual that a year elapsed before the anemia approached the former severe degree. It should be noted that during the period of study the anemia of this patient did not reach the degree of severity that was usual before splenectomy, when the hematocrit value was frequently as low as 16.

The reason that splenectomy was followed by a temporary and partial remission in the hemolytic process is not clear. The studies made of the specimen of blood withdrawn from the splenic vein of our second patient at the time of operation yielded no information which seems of crucial value. All measurements indicate that the average erythrocyte was a little greater in volume and had a slightly smaller diameter and was therefore somewhat thicker than the average erythro-

16. Lintz, R. M.: Toxic Reactions with Gold Salts in Treatment of Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:1629 (July) 1941.

cyte in a peripheral vein. The demonstrable difference in fragility in hypotonic saline solution is a reflection of the increase in mean cell thickness. However, recent studies of blood from a splenic vein in a variety of conditions indicate that these differences, which are slight, are probably within the limits of the normal.[17]

The descriptions of the histopathologic condition of the spleen removed from our patients are also of little aid in postulating the role each organ played in the accelerated destruction of erythrocytes. There is no histologic evidence that their activity was essentially different in the 2 cases. Indeed the similarity of the histologic picture and the partial response to splenectomy indicate that the spleens had a partial or secondary role in destruction of the blood rather than a primary one.

It has not been possible to demonstrate the presence of isohemolysin or isoagglutinin in the blood of either patient by tests in vitro. However, from the studies made following transfusions there is good evidence that in the patient with spherocytosis a potent agent is present which changes the shape and increases the fragility of the transfused cells in hypotonic saline solution overnight. It was also demonstrated that there was a rapid return of the anemic state following transfusion, which must have been due to hemolysis of the transfused cells as well as of the patient's cells.

The hemolytic agent could not be demonstrated in vitro by studies designed to measure the same action it was shown to have in vivo, namely, the effect on the shape and structure of normal cells and on their fragility in hypotonic saline solution. Its nature therefore is not known, but presumably it is the same agent that acts on the patient's erythrocytes. Since it is not easily demonstrable in the peripheral blood there is less difficulty in supposing it to be an immune body type of hemolysin than a simple lytic substance. The supply of the substance is evidently great, however, since the development of spherocytosis and subsequent hemolysis was as rapid after the second transfusion of 1,000 cc. of red cells as after the first, a week previously. These observations confirm the statement of Rous[18] that a hemolytic substance which may not be demonstrable in vitro may produce damage in vivo.

As stated previously, the erythrocytes of the first patient have always shown a tendency toward diminished cell diameter and increased cell thickness. The reasons that erythrocytes lose their bilaterally

17. Watson, C. J., and Paine, J. R.: A Study of the Splenic Venous Blood with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes Before and After Splenic Arterial Injection of Adrenalin, Am. J. M. Sc. **205**:493 (April) 1943.

18. Rous, P.: The Destruction of Red Blood Corpuscles in Health and Disease, Physiol. Rev. **3**:75 (Jan.) 1923.

concave form and become spherocytic are evidently various.[19] It seems probable that the fundamental change is the absorption of fluid and a consequent increase in cell volume. An increase in cell volume has been noted to accompany the development of spherocytosis in stored blood,[20] and Dameshek and Schwartz [21] found evidence of an increase in cell volume concomitant with the development of spherocytosis in experimental hemolytic anemia. In our patient with spherocytosis data have been presented which indicate that following multiple transfusions of red cells a significant increase in mean cell volume occurred along with the development of spherocytosis and increased fragility in hypotonic saline solution. Since an increase in volume through the absorption of fluid would account for the changes in cell morphology observed, it seems likely that the primary effect of the lytic substance was damage to the cell which caused or permitted the absorption of fluid.

While spherocytosis is not a constant feature of hemolytic phenomena, when it is present the factor of increased mechanical fragility is doubtless of considerable importance in accelerating the rate of hemolysis. Shen, Castle and Fleming [22] demonstrated that spherocytic cells exhibit an increased mechanical fragility when rotated with glass beads. They stated their belief that the spherocyte is less able to withstand the changes in shape involved in capillary circulation than is the normal erythrocyte. The mechanical fragility of the cells of our patient with spherocytosis was roughly twelve times normal, while the cells of the second patient without spherocytosis showed a normal mechanical fragility. It is reasonable to suppose, therefore, that hemolysins which produce spherocytosis of erythrocytes accelerate the rate of destruction of blood by increasing the mechanical fragility or by causing further absorption of fluid to the point where rupture of the cell membrane or diffusion of hemoglobin from the cell occurs.

The second patient has never shown spherocytosis or increased fragility of cells in hypotonic saline solution but has always presented a moderate macrocytosis. A macrocytic blood picture has been frequently described in acquired hemolytic anemia and is due to the presence of large numbers of reticulocytes, which always tend to be

19. Dameshek, W., and Miller, E. B.: Pathogenic Mechanisms in Hemolytic Anemias, Arch. Int. Med. **72**:1 (July) 1943.

20. Crosbie, A., and Scarborough, H.: Studies on Stored Blood: VI. Changes in the Erythrocytes During Storage, Edinburgh M. J. **48**:253 (April) 1941.

21. Dameshek, W., and Schwartz, S. O.: Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, Am. J. M. Sc. **196**:769 (Dec.) 1938.

22. Shen, S. C.; Castle, W. B., and Fleming, E. M.: Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes, Science **100**:387 (Oct. 27) 1944.

larger than the mature cells. It seems clear from chart 4 that the transfused erythrocytes were not destroyed with great rapidity in this patient, since it required forty-five days for the hematocrit value to drop from 40 to 35. There is also evidence of a slower rate of destruction of blood following transfusion as shown by the diminished daily output of urobilinogen which occurred in spite of the increase in red cell volume. Josephs [23] has shown that the rate of destruction of blood may decrease sharply following the transfusion of whole blood or plasma in certain types of hemolytic anemia. Since the concentrated red cells used are suspended in approximately 10 per cent plasma it is possible that the diminished hemolysis was due to an antihemolytic substance in normal plasma. Because of the patient's death this possibility was not investigated. However, prior to splenectomy there is no evidence that transfusions of whole blood produced a partial remission in the hemolytic process.

A second possible explanation of the diminished hemolysis should be considered, particularly since the partial remission was so prolonged. The fall in output of urobilinogen followed closely the drop in the percentage of reticulocytes to a normal range. Since the rate of destruction of blood seems so closely related to the rate of formation of blood, it seems possible that the newly formed cell or reticulocyte may have been the most vulnerable to hemolysis. If this suggestion is correct the mechanism of the hemolysis is not explained, but it seems more likely that the defect would lie in cell structure rather than in the selective action of a hemolytic agent. However, it is evident that even when formation of blood was close to normal the excretion of urobilinogen was still several times the normal value, so that it is probable that mature cells were also being destroyed. There is no evidence that the spleen played a part in the hemolysis of young erythrocytes, since the percentage of reticulocytes in the blood from the splenic vein was the same as that in the blood from the peripheral vein. No attempt was made to determine the rate of destruction of the transfused cells as compared to that of the patient's cells; hence no data are at hand to estimate what proportion of the excretion of urobilinogen following transfusion was contributed by the transfused cells.

There seems to be little precedent for the postulate that the immature erythrocytes may be the most susceptible to hemolysis in certain cases of hemolytic anemia, but it is offered as a plausible possibility for further investigation. The reticulocyte has been shown to possess

23. Josephs, H. W.: Studies in Haemolytic Anaemia: II. The Presence of an Anti-Hemolytic Factor in Human Plasma, Bull. Johns Hopkins Hosp. **62**:53 (Jan.) 1938.

certain physical characteristics, aside from the inclusion of a basophilic substance, which differ from those of the mature erythrocyte. In addition to its greater size the reticulocyte has been reported to be more adhesive than the mature cells.[24] Kitchen [25] has demonstrated that it is more susceptible to invasion by Plasmodium vivax than are mature erythrocytes, and Dock and Mermod [26] have presented evidence to show that the serum of patients with untreated pernicious anemia has a selective lytic action for reticulocytes in vitro and that saponin has a selective lytic action on reticulocytes in vivo in rabbits.[27]

The death of our second patient brought to an end observations which might have thrown further light on the relationship of the rate of hemolysis to that of formation of blood and to transfusions of whole blood and plasma. The cause of the cerebral thrombosis is not clear, as no underlying disease of the arterial system was demonstrated. A previous cerebral vascular accident following splenectomy and involving the same area was equally unexplained, since it was not associated with an elevated platelet count or evidence of embolism. It seems possible that the increase in viscosity of the blood following the elevation of the hematocrit value to 48 and the increase of plasma fibrinogen which may have attended the respiratory infection predisposed to a thrombosis which might not otherwise have occurred.

From the data accumulated there is no evidence that the fat content of the diet had any effect on the rate of hemolysis which might be considered important from a therapeutic standpoint. In retrospect the periods of observation seem rather brief, particularly with regard to the second patient, who was changed from a diet high in fat to one low in fat. However, after the transfusions he returned to his normal diet, which was high in fat content, and yet exhibited a reduced output of urobilinogen for a long period of time.

SUMMARY AND CONCLUSIONS

The histories of 2 patients with chronic hemolytic anemias have been presented. One patient has always exhibited spherocytosis and an increased fragility of red blood cells in hypotonic saline solution. The onset of the disease in her case followed the therapeutic injection

24. Davidson, L. S. P.: The Basophilic Substance of the Erythrocyte, Edinburgh M. J. **37**:425 (Aug.) 1930.

25. Kitchen, S. F.: The Infection of Reticulocytes by Plasmodium Vivax, Am. J. Trop. Med. **18**:347 (July) 1938.

26. Dock, W., and Mermod, C.: Hemolysins to Which Reticulocytes Are Especially Vulnerable in the Plasma of Primary Anemia, Proc. Soc. Exper. Biol. & Med. **32**:373 (Nov.) 1934.

27. Mermod, C., and Dock, W.: Fragility and Maturation of Reticulocytes, Arch. Int. Med. **55**:52 (Jan.) 1935.

of colloidal gold for arthritis. No hemolytic agent could be demonstrated by tests in vitro, but after a massive transfusion of red cells it has been shown that transfused erythrocytes acquire an increased fragility in hypotonic saline solution within twenty-four hours after injection. This change is accompanied by an increase in mean cell volume and a decrease in mean cell diameter. It seems likely that the lytic substance produces these changes by damaging the cell so as to cause absorption of fluid.

The second patient described has never exhibited spherocytic erythrocytes, and the fragility of red blood cells in hypotonic saline solution has always been normal. Restoration of the circulating hemoglobin to a normal level by multiple transfusions of red blood cells was followed by evidence of diminished hemolysis. While this effect might have been due to an antihemolytic factor in human plasma, the suggestion is made that, since the amount of output of pigment is so closely associated with formation of blood, it was the reticulocytes, or newly formed cells, which were the most susceptible to hemolysis in this patient. This suggests that the defect was inherent in the patient's erythrocytes, although other possibilities must be considered.

No information was gained from either patient to indicate that the fat content of the diet was of therapeutic importance in the rate of blood destruction. Of some therapeutic significance is the fact that 1 patient was not benefited by multiple transfusions while the other was able to return to work and exhibited a diminished rate of blood destruction following the restoration of the circulating hemoglobin to normal level.

CONCENTRATED HUMAN ALBUMIN IN THE TREATMENT OF SHOCK

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WHOLE blood is the best replacement fluid for treating patients with acute hemorrhage. It has the disadvantage of being difficult to preserve and bulky to transport, and it must be typed before it is administered. In an effort to overcome these difficulties plasma has been used extensively. It has the advantage that it can be given without typing. However, it is bulky to transport in liquid or frozen state, and it is easily contaminated by bacteria. When dried, plasma is stable, but time must be taken to restore it to liquid state. A substitute for plasma which could be packaged in concentrated form, which did not need to be preserved by drying or freezing, which was stable under all types of motion produced by ships or tanks and which could be given rapidly in large quantities without reaction was obviously needed. On theoretic grounds the solution of concentrated human albumin made possible by the work of Cohn and his colleagues at Harvard University appeared to be the ideal substitute for plasma.[1]

A test of the usefulness of human albumin [2] as a substitute for plasma has been made at Grady Hospital by observing the effects of giving it intravenously to 7 normal subjects and to 34 patients with circulatory failure.

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Emory University School of Medicine.

1. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: I. The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation **23**:417, 1944.

2. The products of plasma fractionation employed in this work were developed from blood, collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

METHODS

The technics used in this study have been described in detail elsewhere.[3] A catheter was introduced into the right atrium by way of the antecubital vein to obtain samples of mixed venous blood and to measure the mean atrial pressure in millimeters of water. The consumption of oxygen was measured by analyzing a two minute sample of expired air collected in a Douglas bag. Samples of arterial blood and optical recording of arterial pressure were obtained by placing an inlying needle in the femoral artery. The oxygen content of the arterial and right atrial blood was determined by the method of Van Slyke.[4] The cardiac output was calculated by the utilization of the Fick principle. A point 5 cm. posterior to the fourth costochondral junction was taken as the zero point for calculating the right atrial pressure. The plasma volume was measured by injecting the blue dye T-1824 (Evans' blue) and determining its concentration either in a series of samples or in a single sample collected ten minutes after the dye was injected. If there was no evidence of further bleeding, the change in blood volume after therapy was usually estimated from the change in the hematocrit reading. Heparin was used as the anticoagulant in the hematocrit tubes. The concentration of protein was measured by the falling drop method. Since the output of the heart varies with the size of the person, the cardiac indexes rather than the output are frequently referred to in this paper. The cardiac index is the cardiac output measured in liters of blood per minute per square meter of body surface.

RESULTS

No untoward effects were noted. None of the patients experienced chills, fever, urticaria, pulmonary edema or circulatory collapse.

NORMAL SUBJECTS

Seven normal subjects received 1 liter of a 5 per cent solution of human albumin intravenously (see table). The time required for the infusion ranged from fifteen to thirty-one minutes. Two consistent changes were noted. The atrial pressure always rose, and the hematocrit reading and concentration of hemoglobin always fell. The arterial pressure, cardiac rate, consumption of oxygen and arteriovenous oxygen difference showed no consistent change. The cardiac output

3. Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization: Normal Values with Observations on the Effect of Anxiety and Tilting, J. Clin. Investigation **24**:326, 1945.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

Patient	Diagnosis	Age	Sex	Surface Area, Sq. M.	Oxygen Consumption, Cc. per Min. per Sq. M.	Oxygen Saturation of Arterial Blood, per Cent	Arterial Oxygen Content, Vol. per Cent	Mixed Venous Oxygen Content, Vol. per Cent
	Normal Subjects							
L. R.	Control	22	M	1.95	116	..	18.2	14.9
	Immediately after albumin*				108	..	15.4	11.8
	70 minutes after albumin				133	..	16.0	12.7
C. P.	Control	32	M	1.69	151	..	16.4	12.9
	Immediately after albumin				170	..	15.2	11.7
F. L.	Control	41	F	1.61	117	..	13.8	10.4
	10 minutes after albumin				119	..	10.9	7.9
	55 minutes after albumin				137	..	11.0	8.0
J. B.	Control	36	M	2.0	127	..	17.4	13.8
	55 minutes after albumin				111	..	14.8	12.3
L. L.	Control	16	M	1.73	142	..	17.0	11.4
	Immediately after albumin				130	..	14.4	10.5
	60 minutes after albumin				124	..	15.8	11.8
W. W.	Control	57	M	1.73	129	..	16.0	11.8
	Immediately after albumin				121	..	13.0	10.6
	60 minutes after albumin				120	..	13.3	11.0
A. W.	Control	33	M	1.74	120	..	12.2	9.6
	Immediately after albumin				127	..	10.1	5.2
	100 minutes after albumin				118	..	....	....
	Patients with Hemorrhage							
C. R.	Bleeding peptic ulcer	56	M	2.09	...	..	....	....
	Immediately after 25 Gm. albumin‡				...	..	....	....
	50 minutes after albumin				...	..	....	....
A. D.	Lacerations	33	F	1.64	112	..	11.9	5.8
	20 minutes after 50 Gm. albumin				...	..	...	....
	60 minutes after albumin				113	..	9.2	6.2
L. D.	Lacerations	36	M	1.60	136	..	16.7	11.9
	Immediately after 50 Gm. albumin				...	..	....	....
	30 minutes after albumin				157	..	13.8	10.4
C. J.	Lacerations	39	M	1.76	127	..	14.9	6.8
	Immediately after 50 Gm. albumin				...	..	....	....
	30 minutes after albumin				142	..	12.4	7.7
L. A.	Lacerations	15	M	1.68	113	..	13.1	8.1
	Immediately after 50 Gm. albumin				...	..	....	....
	30 minutes after albumin				126	..	11.8	8.2
	5 minutes after 500 cc. saline				126	..	10.9	8.0
A. L. C.	Lacerations	21	M	1.92	...	..	....	....
	35 minutes after 50 Gm. albumin				...	..	....	....
F. G.	Lacerations	25	F	1.75	...	..	....	....
	Immediately after 50 Gm. albumin				...	..	....	....
	15 minutes after albumin				...	..	....	....
W. B.	Lacerations	30	M	1.80	...	..	....	....
	Immediately after 50 Gm. albumin				...	..	....	....
	20 minutes after albumin				...	..	....	....
H. F.	Lacerations	45	M	1.68	116	..	14.5	10.7
	Immediately after 50 Gm. albumin				...	..	12.6	10.0
	25 minutes after albumin				...	..	....	....
H. W.	Lacerations	33	M	1.80	...	..	....	....
	Immediately after 50 Gm. albumin				...	..	....	....
	60 minutes after albumin				...	..	....	....
T. A.	Lacerations	30	M	2.0	...	..	....	....
	Immediately after 50 Gm. albumin				...	..	....	....
	60 minutes after albumin				...	..	....	....
M. Z.	Lacerations	22	F	1.46	111	..	11.9	6.8
	20 minutes after 50 Gm. albumin				145	..	10.4	7.4
J. H.	Lacerations	34	M	1.72	...	..	....	....
	Immediately after 50 Gm. albumin				...	..	....	....
	30 minutes after albumin				...	..	....	....

Arterio-venous Oxygen Difference, Vol. per Cent	Cardiac Output, Liters per Min.	Cardiac Index, Liters per Min. per Sq. M.	Hemoglobin, Gm. per 100 Cc.	Hematocrit Reading	Systolic Pressure Mm. of Hg	Diastolic Pressure Mm. of Hg	Mean, Mm. of Hg	Pulse Rate, Beats per Min.	Peripheral Resistance Absolute Units	Total Plasma Protein, Gm. per 100 Cc.	Atrial Pressure, Mm. Water	Blood Volume, Cc. per Sq. M.	Increase in Blood Volume, Cc. per Gm. Albumin	Blood Alcohol, Mg. per 100 Cc.	Additional Fluids Given, Cc. Saline Solution
Normal Subjects															
3.3	6.9	3.5	14.5	41	127	69	91	65	1,050	6.0	40	.....	..	..	...
3.5	6.0	3.0	12.2	36	120	68	87	73	1,200	5.7	110	.....	..	..	...
3.3	7.8	4.0	12.7	39	...	..	..	..	.....	5.9	75	.....	..	..	...
3.5	7.3	4.3	....	45	110	65	81	100	880	5.9	15	.....	..	..	...
2.7	7.8	4.6	....	37	113	65	80	105	820	5.6	120	.....	..	..	...
2.4	5.5	3.4	10.0	34	136	78	98	94	1,420	7.2	—15	.....	..	..	...
3.0	6.3	3.9	8.8	27	127	72	92	94	1,170	6.7	45	.....	..	..	...
3.0	7.5	4.6	8.9	28	140	80	100	84	1,060	6.8	15	.....	..	..	...
2.6	7.1	3.6	14.2	46	125	75	88	88	1,000	6.8	—15	.....	..	..	...
2.5	8.7	4.4	12.6	39	155	79	103	60	950	6.5	30†	.....	..	..	...
3.6	4.4	2.5	14.8	43	119	68	83	53	1,510	5.5	60	2,560	..	..	...
2.9	5.7	3.3	11.5	33	142	78	99	60	1,390	5.0	190	3,280	..	..	...
4.0	5.4	3.1	13.8	37	142	78	98	52	1,450	5.6	90	2,980	..	..	...
4.2	5.3	3.1	12.7	38	163	86	113	66	1,700	5.9	20	2,600	..	..	...
2.4	8.8	5.1	10.9	29	166	84	113	66	1,030	5.5	90	3,360	..	..	...
2.3	9.0	5.2	10.4	32	150	77	105	60	930	5.8	50	3,050	..	..	...
2.6	8.1	4.6	9.5	32	107	47	66	60	660	6.1	5	.....	..	..	...
4.9	4.5	2.6	8.1	27	107	47	69	71	1,220	6.2	105	.....	..	..	...
...	...	...	7.8	..	...	..	..	..	.....	6.4	45	.....	..	..	...
Patients with Hemorrhage															
...	...	...	....	22	130†	58	..	90	.....	4.4	...	1,900	..	..	...
...	...	...	....	..	106†	46	..	90	.....	...	...	.....	..	..	...
...	...	...	....	19	104†	56	..	84	.....	4.5	...	2,210	27	..	...
6.1	2.9	1.8	9.8	33	68	43	53	107	1,490	5.4	5	.....	..	180	...
...	...	...	7.8	26	98	60	72	100	.....	6.1	40	.....	..	..	...
3.0	6.2	3.8	7.3	24	102	59	75	100	960	5.6	40	.....	..	..	200
4.8	4.5	2.8	12.7	38	91	65	69	96	1,230	5.6	15	2,310	..	348	...
...	...	...	11.4	32	142	83	104	100	.....	6.2	85	2,880	18	..	180
3.4	7.6	4.8	10.8	31	139	77	100	96	1.050	5.9	85	2,940	..	..	...
8.1	2.8	1.6	12.1	36	61	33	41	80	1,160	5.4	10	.....	..	..	...
..	...	...	10.0	32	...	..	..	..	.....	6.0	30	.....	..	..	...
4.7	5.3	3.0	10.0	31	75†	50	..	67	.....	5.8	55	.....	..	..	300
5.0	3.8	2.3	10.1	33	80	58	70	88	1,470	4.9	0	2,020	..	..	...
..	...	...	....	31	...	..	..	..	.....	6.0	50	2,320	..	..	...
3.6	5.9	3.5	8.8	29	107	61	76	79	1,070	5.6	20	2,440	10	..	150
2.9	7.3	4.3	8.2	27	124	65	85	79	930	5.0	70	2,620	14	..	500
...	...	...	....	42	80†	60	..	100	.....	5.4	...	2,450	..	..	...
...	...	...	....	39	127†	74	..	96	.....	6.2	...	2,600	6	..	...
...	...	...	.....	35	88†	48	..	110	.....	5.1	...	1,800	..	219	...
...	...	...	....	..	110†	64	..	106	.....	...	...	.....	..	..	...
...	...	...	....	30	...	..	..	..	.....	5.6	...	2,080	10	..	...
...	...	...	....	40	80†	54	..	68	.....	5.0	...	2,800	..	..	...
...	...	...	....	..	112†	74	..	72	.....	...	...	.....	..	..	...
...	...	...	....	34	116†	66	..	66	.....	5.2	...	3,270	17	..	...
3.8	5.1	3.1	11.1	36	90	56	68	88	1,070	5.6	20	2,320	..	180	...
2.6	...	...	9.7	31	110	62	81	100	.....	5.6	60	2,670	12	..	...
...	...	...	....	30	...	..	..	..	.....	...	...	2,800	16	..	300
...	...	...	....	35	47	28	37	99	.....	...	...	.....	..	62	...
...	...	...	....	32	88	52	61	114	.....	...	...	.....	..	..	...
...	...	...	....	30	84	48	59	84	.....	...	...	.....	..	..	...
...	...	...	....	40	86	54	68	96	.....	...	...	2,630	..	169	...
...	...	...	....	35	106	60	79	96	.....	...	...	2,960	13	..	...
...	...	...	....	34	110	64	80	96	.....	...	...	3,050	17	..	...
5.1	3.2	2.2	10.2	32	86	47	59	72	1,480	5.8	5	1,820	..	..	...
3.0	7.0	4.8	7.8	25	130	75	96	96	1,120	6.5	45	2,300	14	..	125
...	...	..	....	47	92†	66	..	108	.....	6.1	...	1,980	..	314	...
...	...	...	....	42	88†	66	..	104	.....	6.7	...	2,200	8	..	...
...	...	...	....	40	106†	72	..	106	.....	6.7	...	2,310	12	..	...

Patient	Diagnosis	Age	Sex	Surface Area, Sq. M.	Oxygen Consumption, Cc. per Min. per Sq. M.	Oxygen Saturation of Arterial Blood, per Cent	Arterial Oxygen Content, Vol. per Cent	Mixed Venous Oxygen Content, Vol. per Cent
	Patients with Injuries of Chest							
L. D.	Stabbed chest §	27	M	1.65	167	..	14.7	10.9
	Immediately after 50 Gm. albumin				...	..	....	...
	38 minutes after albumin				167	..	14.1	10.2
O. M.	Stabbed chest	50	F	1.46	122	..	9.4	5.7
	25 minutes after 50 Gm. albumin				123	..	7.4	4.2
W. W.	Stabbed chest	33	M	1.83	192	..	16.2	10.6
	12 minutes after 50 Gm. albumin				189	..	16.5	11.6
	35 minutes after albumin				...	..	....	...
A. E.	Fractured ribs	71	F	1.57	104	67	8.2	2.5
	5 minutes after 25 Gm. albumin				...	..	7.4	2.2
	10 days later				138	92	11.5	6.9
W. L. T.	Stabbed chest	52	M	1.87	107	..	13.6	9.4
	35 minutes after 50 Gm. albumin				107	..	12.1	8.4
P. D.	Stabbed chest	34	M	1.67	151	88	15.0	10.1
	5 minutes after 50 Gm. albumin				188	..	13.2	9.1
V. S.	Stabbed chest	23	F	1.76	...	..	....	...
	Immediately after 50 Gm. albumin				...	..	....	...
	30 minutes after albumin				...	..	....	...
	Patients with Stabbed Heart							
N. B.	Before therapy	59	M	1.72	180	..	12.8	7.9
	Immediately after 25 Gm. albumin in 500 cc. saline sol				179	..	11.7	6.9
	68 minutes after albumin				...	..	....	...
S. W.	Before therapy	32	M	1.80	111	..	16.2	10.4
	Immediately after 50 Gm. albumin				109	..	14.1	9.4
	Patients with Miscellaneous Conditions							
A. W.	Dehydration—ileostomy	34	F	1.32	116	..	12.2	9.4
	3 hours after 50 Gm. albumin and 1,500 cc. saline sol				164	..	8.8	6.8
W. G.	Extensive burns	58	F	1.60	141	..	16.1	10.9
	After 500 cc. saline sol				113	..	15.7	9.8
	After 3,000 cc. saline sol and dextrose				112	..	15.6	10.5
	After 50 Gm. albumin				169	..	13.2	8.9
B. L.	Extensive burns	80	..	1.2	108	..	18.2	8.8
	25 minutes after 50 Gm. albumin				133	..	15.2	8.9
W. J.	Extensive burns	..	..	1.52	172	..	17.5	13.5
	43 minutes after 50 Gm. albumin				238	..	16.6	12.4
	2 hours later				173	..	15.3	13.4
RM. H.	Reaction to oxophenarsine hydrochloride	16	F	1.92	176	..	18.1	9.6
	Immediately after 50 Gm. albumin				...	..	....	....
	Immediately after 25 Gm. albumin				...	..	....	....
	37 minutes after albumin				180	..	17.0	10.0
T. F.	Pneumonia	31	M	1.81	210	..	19.3	5.0
	12 minutes after 75 Gm. albumin				329	..	16.2	9.2
	Immediately after 850 cc. saline sol				350	..	15.6	9.3
M. B.	Pneumonia	39	F	1.41	149	..	17.5	13.5
	Immediately after 25 Gm. albumin and 1,000 cc. saline sol.				145	..	14.8	10.7
F. S.	Acute peritonitis	39	M	2.08	136	..	17.9	11.6
	5 minutes after 75 Gm. albumin				118	..	15.8	12.1
	40 minutes after albumin				...	..	....	....
S. K.	Periurethral abscess—drained	39	M	1.91	143	..	12.3	5.8
	Immediately after 75 Gm. albumin				147	..	9.3	5.5
E. J.	After nephrectomy for tuberculous kidney	30	F	1.31	116	..	15.6	10.0
	5 minutes after 50 Gm. albumin				118	..	12.9	8.6
W. H.	After operation for gunshot wound in abdomen	44	M	1.97	205	..	17.8	7.4
	5 minutes after 75 Gm. albumin				236	..	14.4	9.1

* All normal subjects received 1,000 cc. containing 50 Gm. of human serum albumin in isotonic solution of sodium chlorid

† By auscultatory methods.

‡ All patients received 25 per cent human serum albumin unless otherwise stated.

§ All initial studies were made prior to albumin therapy.

Before and After Receiving Human Albumin Solution—Continued

Arterio-venous Oxygen Difference, Vol. per Cent	Cardiac Output, Liters per Min.	Cardiac Index, Liters per Min. per Sq. M.	Hemoglobin, Gm. per 100 Cc.	Hematocrit Reading	Systolic Pressure Mm. of Hg	Diastolic Pressure Mm. of Hg	Mean, Mm. of Hg	Pulse Rate, Beats per Min.	Peripheral Resistance Absolute Units	Total Plasma Protein, Gm. per 100 Cc.	Atrial Pressure, Mm. Water	Blood Volume, Cc. per Sq. M.	Increase in Blood Volume, Cc. per Gm. Albumin	Blood Alcohol, Mg. per 100 Cc.	Additional Fluids Given, Cc. Saline Solution
Patients with Injuries of Chest															
10.0	7.2	4.4	12.5	42	88	56	66	88	730	5.8	20	.....	..	155	359
...	...	...	11.3	38	130	82	95	112	.....	6.5	50	.....	12	..	...
10.0	8.6	5.2	10.9	37	120	72	88	108	820	6.2	50	.....	..	..	...
5.7	4.8	3.3	8.2	26	80	48	62	68	1,030	5.6	5	1,770	..	..	...
4.3	5.5	3.8	6.1	20	90	58	71	75	1,030	5.5	55	2,310	16	..	400
10.0	6.3	3.4	14.0	44	63	45	51	75	650	5.2	45	3,160	..	52	...
11.8	9.3	5.1	13.0	40	99	65	71	84	610	5.6	95	3,480	12	..	...
...	...	...	12.6	40	...	..	..	..	.....	5.5	...	.....	..	..	200
2.6	2.9	1.8	8.6	29	105	45	54	103	1,250	5.1	70	1,710	..	..	...
2.2	...	...	7.8	26	103	45	52	103	.....	5.2	120	1,870	10	..	...
6.8	4.7	3.0	8.9	29	140	60	87	71	1,480	...	10	1,960	..	..	...
8.4	4.8	2.6	10.0	32	71	42	50	75	830	5.4	25	2,060	..	290	...
8.4	5.4	2.9	8.9	28	122	63	83	84	1,230	5.8	65	3,080	16	..	150
10.1	5.1	3.1	13.5	40	77	46	54	77	850	4.8	65	2,970	..	90	...
9.1	7.7	4.6	12.3	35	100	63	74	97	770	5.6	140	3,360	13	..	175
...	...	...	....	36	80†	50	..	88	.....	5.6	...	2,160	..	250	...
...	...	...	....	32	76†	60	..	100	.....	6.0	...	2,400	9	..	...
...	...	...	....	31	88†	62	..	110	.....	6.0	...	.....	..	..	...
Patients with Stabbed Heart															
7.0	5.4	3.2	11.0	34	84-100	60-68	72	88	1,070	6.2	135	.....	..	360	...
6.3	6.6	3.8	10.7	32	92-104	68	77	88	930	6.2	190	.....	..	..	...
...	...	...	....	32	...	..	..	..	.....	6.2	...	.....	..	..	...
10.4	3.4	1.9	17.7	45	83-100	51-54	64	88	1,500	5.9	160	.....	..	230	...
8.8	4.2	2.3	15.4	39	98-110	60	73	84	1,390	5.6	255	.....	..	..	...
Patients with Miscellaneous Conditions															
9.4	5.5	4.2	10.4	33	83	49	61	107	880	6.4	—10	2,500	..	..	...
6.8	10.9	8.3	....	23	109	60	81	111	590	5.3	+90	3,700	32	..	...
10.4	4.3	2.7	14.9	40	159	90	117	115	2,160	6.4	20	.....	..	..	...
8.8	5.0	1.9	13.0	38	148	84	98	94	2,510	5.9	10	.....	..	..	...
10.5	5.1	3.5	2.2	10.6	39	134	84	95	136	2,180	5.9	10	.....	..	..
8.9	4.3	5.9	5.7	....	33	180	96	126	136	1,710	5.5	55	.....	..	..
8.3	9.4	1.4	1.2	14.9	46	92	62	66	88	3,770	7.3	— 5	.....	..	..
8.9	6.3	2.5	2.1	12.8	40	154	88	105	88	3,310	7.8	+25	.....	..	..
13.5	4.0	6.5	4.3	15.5	50	140	89	107	167	1,320	6.9	0	.....	..	..
12.4	4.2	8.6	5.7	13.5	44	145	86	114	178	1,060	6.8	20	.....	..	..
13.4	1.9	13.9	9.1	....	..	130	89	103	188	690	6.5	10	.....	..	..
9.6	8.5	4.0	2.1	13.8	45	94	60	68	160	1,360	4.6	—10	.....	..	..
...	...	...	...	12.1	40	84	52	62	148	.....	5.7	+ 5	.....	..	..
...	...	...	...	11.5	37	89	55	66	144	.....	5.1	30	.....	..	..
10.0	7.0	4.9	2.6	10.7	36	96	58	70	150	1,140	4.9	10	.....	..	..
5.0	14.3	2.7	1.5	16.2	51	76	54	59	180	1,750	...	—25	3,100	..	..
9.2	7.9	8.5	4.7	13.3	44	101	63	73	168	690	...	+ 5	3,660	13	..
9.2	6.4	9.9	5.5	12.2	41	125	80	93	160	750	...	30	3,940	20	..
13.5	4.0	5.3	3.8	12.8	41	107	60	69	79	1,040	5.5	30	.....	..	..
10.7	4.1	5.0	3.5	10.9	36	107	57	71	67	1,140	5.0	105	.....	..	..
11.6	6.3	4.5	2.2	14.4	42	77	48	54	125	960	6.4	10	2,700	..	..
12.1	3.7	6.6	3.2	12.6	37	81	50	60	115	730	7.0	65	3,100	11	..
...	...	...	...	....	36	84	54	61	115	.....	6.6	70	3,200	12	..
5.8	6.4	4.3	2.2	9.6	30	82	49	56	107	1,040	5.6	— 5	2,140	..	..
5.5	3.7	7.6	4.0	7.7	24	93	49	62	94	670	6.2	+ 3	2,720	15	..
10.0	5.6	2.7	2.1	12.4	41	103	59	72	97	2,130	6.9	5	1,900	..	..
8.6	4.3	3.6	2.7	10.0	32	111	59	79	94	1,750	7.2	30	2,410	10	..
7.4	10.4	3.9	2.0	13.8	40	109	65	72	150	1,480	6.7	—35	.....	..	..
9.1	5.3	8.8	4.5	11.6	35	109	59	72	140	650	7.1	25	.....	..	..

tended to increase, though at times it remained unchanged or decreased. When the cardiac output increased, it did not appear to parallel the rise in atrial pressure, for it persisted as the atrial pressure fell.

HEMORRHAGE

Studies were made on 13 patients with circulatory insufficiency following acute hemorrhage (see table). Twelve of these patients had lost blood following knife wounds and one had bled from a peptic ulcer. All received 50 Gm. of a 25 per cent solution of human albumin except 1, who received 25 Gm. of albumin. Five of the patients were given from 125 to 300 cc. of isotonic solution of sodium chloride intravenously in addition to the albumin. The cardiac output was determined for 6 patients before any therapy, and for 5 of these after the administration of albumin. The time which elapsed between therapy and determinations of cardiac output varied from twenty to sixty minutes. The initial cardiac index varied from 1.6 to 3.1, with an average of 2.3. Following administration of albumin the cardiac index varied from 3.0 to 4.8, with an average of 4.0. The arterial systolic pressure increased in each instance except in patient C. R. The increase in cardiac output was proportionally greater than the increase in the mean arterial pressure, so that the peripheral resistance fell. There was no consistent change in heart rate.

Hemodilution occurred in each instance as reflected by the hematocrit reading and the concentration of hemoglobin and volume of plasma when measured. The volume of plasma was measured in 10 of the patients and found to be below the normal expected level in 8. The average increase in volume of blood per square meter of body surface following the administration of albumin was 417.0 cc. The average increase in volume of blood per gram of albumin given was 15.0 cc. Hematocrit studies showed that the hemodilution took place rapidly during and immediately after the administration of the albumin and continued at a somewhat lower rate during the hour following the therapy. There seemed to be little difference in the effect of the albumin in patients who received no added fluid and in those receiving up to 300 cc. of isotonic solution of sodium chloride.

INJURIES OF THE CHEST

Seven patients with rents of the parietal pleura were studied (see table). Six of these patients had received knife wounds shortly before they came to the hospital. The seventh, A. E., had received multiple fractures of the ribs as the result of an automobile accident twelve hours prior to the time of study. All of the patients had clinical evidence of circulatory insufficiency. The systolic arterial pressure was

below 100 mm. of mercury in each instance except that of patient A. E. In A. E. and P. D. the percentage saturation of the arterial blood with oxygen was 67 and 88 respectively.

Studies of cardiac output were made on 6 patients prior to any therapy and on 5 of these after the administration of albumin. Fifty grams of albumin in a 25 per cent solution was given to all except 1, who was given 25 Gm. The time which elapsed between therapy and measurement of the cardiac output varied from five to thirty-eight minutes. The initial cardiac index in the patients studied before and after therapy varied from 2.6 to 4.4, with an average of 3.4. The average cardiac index after therapy was 4.3.

The arterial pressure increased in each patient after the administration of albumin except in patient A. E. The peripheral resistance tended to be decreased before therapy and did not change significantly following therapy. The right atrial pressure consistently increased, and the heart rate of each patient increased except that of A. E., which remained unchanged.

The volume of plasma was measured in 6 of the patients and found to be below the expected normal value in 3. Hemodilution occurred in each patient as evidenced by the fall in hematocrit reading, in concentration of hemoglobin and in volume of plasma when measured. The average increase in volume of blood per gram of albumin was 12.6 cc.

STAB WOUND OF THE HEART

Two patients with hemopericardium resulting from penetrating wounds were studied (see table). N. B. was stabbed with an ice pick and S. W. with a knife. Both patients showed clinical signs of circulatory insufficiency, distended veins of the neck, paradoxic pulse and only slight excursions of the heart borders when examined fluoroscopically. Both cases were complicated by acute alcoholism.

Studies of cardiac output were made before and after the administration of human albumin. N. B. had a cardiac index of 3.2 initially and 3.8 after the intravenous administration of 25 Gm. of albumin in 500 cc. of isotonic solution of sodium chloride. The right atrial pressure increased from 135 to 190 mm. of water, and the arterial pressure became less paradoxic.

S. W. had a cardiac index of 1.9, which increased to 2.3 after the administration of 200 cc. of 25 per cent solution of human albumin intravenously. The right atrial pressure increased from 160 to 255 mm. of water, and his arterial pressure became less paradoxic. There was no significant change in heart rate, and the peripheral resistance was slightly lower in each instance following therapy. Hemodilution occurred in each instance as evidenced by the decrease in the hematocrit reading and in the concentration of hemoglobin.

In this clinic it is believed that the use of intravenous solutions results in improvement of the circulation in patients with pericardial tamponade from stab wound of the heart, even though the atrial pressure is elevated before therapy is started.[5] A further rise in atrial and venous pressure by increasing the volume of blood allows the heart to fill better either by forcing blood out of the pericardial sac through the pericardial rent or by slight stretching of the pericardium. Albumin appears to be the ideal material to use for this purpose in the emergency clinic.

A heterogenous group of patients with clinical signs of circulatory insufficiency were studied before and after the intravenous administration of human albumin. We formed the clinical impression that all had hemoconcentration even though the hematocrit readings were below normal in some instances. In the patients with burns and the reaction to oxophenarsine hydrochloride, the hemoconcentration resulted from extravasation of plasma; in the remainder, from dehydration. The group consisted of 1 patient with loss of fluid from a stoma of the ileum, 3 patients with extensive burns of the body surface, 1 patient with generalized edema following the intravenous injection of oxophenarsine hydrochoride, 2 patients with pneumococcic pneumonia, 1 patient with generalized peritonitis which was thought to have been due to a ruptured appendix, 1 patient with hemorrhage after drainage of a periurethral abscess, 1 patient who had recently had the right kidney removed for renal tuberculosis and 1 patient who had been operated on for a gunshot wound in the abdomen.

One patient was given 25 Gm. of albumin in a 25 per cent solution: 5 were given 50 Gm., and 5 were given 75 Gm. The average arteriovenous oxygen difference before therapy was 7.0, whereas after therapy the average was 4.4. The average cardiac index was 2.6 and 4.5 respectively before and after therapy. The mean arterial pressure increased after therapy except in 1 instance, in which it remained the same. The heart rate decreased in 7 patients, increased in 3 and did not change in 1.

COMMENT

The data on the normal subjects are of considerable interest. They demonstrate again that a considerable increase in volume of blood over the normal level may be produced without an appreciable rise in arterial pressure. The lack of correlation between the atrial pressure

5. (*a*) Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: Pericardial Tamponade from Stab Wound of the Heart and Pericardial Effusion or Empyema: A Study Utilizing the Method of Right Heart Catheterization, Am. Heart J., to be published. (*b*) Cooper, F. W., Jr.; Stead, E. A., Jr., and Warren, J. V.: The Beneficial Effect of Intravenous Infusions in Acute Pericardial Tamponade, Ann. Surg. **120**:822, 1944.

and the cardiac output noted in these data has been confirmed by observations concerning a large series of patients whose atrial pressure was raised by the rapid intravenous administration of isotonic solution of sodium chloride.[6] The significance of these observations will be fully discussed elsewhere.

The results of therapy in patients with hemorrhage were uniformly good. These patients demonstrate the simplest form of circulatory failure produced by injury. Blood is lost from the vascular bed; the atrial pressure and the cardiac output fall, and the arterial pressure finally reaches a low level. The cardiac output falls to a greater degree than does the arterial pressure, indicating persistence of arteriolar tone and well maintained peripheral resistance. When the volume of blood is restored, the cardiac output rises and the peripheral resistance decreases.

The patients with wounds of the pleura showed good hemodilution in response to the administration of albumin. Though these patients appeared clinically to have the same type of circulatory failure as did the patients with simple hemorrhage, analysis of the data on 13 patients with wounds of the chest shows certain significant differences.[7] The fall in cardiac output in these patients was not striking and was proportionately much less than the fall in arterial pressure. The atrial pressure did not usually fall below the normal level. This type of circulatory collapse has been shown to be the result of reflex loss of arteriolar tone.[8] In these patients loss of blood probably played a secondary role in producing the shock picture. A part of the sharp rise in arterial pressure observed after the administration of the albumin may well have occurred spontaneously.

The results of therapy in the patients with burns, dehydration and infection were satisfactory. The clinical condition of the patients improved as the circulation became more adequate.

Measurements of the blood volume of 21 patients were made before and after therapy. Between 100 and 200 cc. of isotonic solution of sodium chloride was always given to the patients in whom the cardiac output was measured, because the lumen of the catheter was kept patent by

6. Unpublished data from this laboratory.

7. Merrill, A. J.; Warren, J. V.; Stead, E. A., Jr., and Brannon, E. S.: The Circulation in Penetrating Wounds of the Chest: A Study by the Method of Right Heart Catheterization, Am. Heart J., to be published.

8. (*a*) Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: The Effect of Venesection and the Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observations on Acute Circulatory Collapse in Three Instances, J. Clin. Investigation **24**:337, 1945. (*b*) Barcroft, H.; Edholm, O. G.; McMichael, J., and Sharpey-Schafer, E. P.: Posthemorrhagic Fainting: Study by Cardiac Output and Forearm Flow, Lancet **1**:489, 1944. Merrill, Warren, Stead and Brannon.[7]

a slow continuous drip. The average increase in plasma volume produced by 1 Gm. of albumin was 14.0 cc. Four of the 21 were patients with dehydration who were given a 25 per cent solution of albumin with a minimum of added fluid. In these 4 patients the average increase in volume of plasma produced by 1 Gm. of albumin was 13.0 cc. It appears that fluid is drawn into the blood stream in effective amounts even in the presence of moderate dehydration. In a preliminary report from this laboratory it was found that 16 cc. of fluid was retained for each gram of albumin.[9] Other workers have reported an average increase in volume of 17.4 cc. per gram of albumin.[10] The increase in volume of blood per gram of albumin will be influenced by the degree of loss of plasma, the state of hydration of the patient and the amount of fluid given parenterally or by mouth before, during or after the infusion of albumin. In a few hours the body can add or remove enough protein from the blood stream significantly to change the volume of plasma. If excess albumin is given, it may be removed by the body, a circumstance which would alter the apparent efficiency of the albumin.

The concentrated solution of albumin was given rapidly to most of the patients. To 11 patients 50 Gm. was administered in fifteen minutes or less. The speed with which a large amount of protein can be given without reaction is one of the most attractive features of albumin therapy.

Recently it has been emphasized that albumin is not as useful in the treatment of shock as is whole blood.[11] With this we are in agreement. Neither plasma nor albumin is a substitute for whole blood. Albumin is nevertheless an extremely useful substitute for plasma. From the standpoint of speed and convenience of administration, convenient packaging, small bulk, stability under varying temperatures and absence of bacterial contamination, concentrated albumin is ideal. In civilian practice, where whole blood and plasma are readily available, albumin may not be used extensively in the treatment of shock, but under the

9. Warren, J. V.; Stead, E. A., Jr.; Merrill, A. J., and Brannon, E. S.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: IX. The Treatment of Shock with Concentrated Human Serum Albumin; a Preliminary Report, J. Clin. Investigation **23**:506, 1944.

10. Heyl, J. T.; Gibson, J. G., II, and Janeway, C. A.: Studies on the Plasma Proteins: V. The Effect of Concentrated Solutions of Human and Bovine Serum Albumin on Blood Volume After Acute Blood Loss in Man, J. Clin. Investigation **22**:763, 1943.

11. Cournand, A.; Noble, R. P.; Breed, E. S.; Lauson, H. D.; Baldwin, E. D.; Pinchot, G. B., and Richards, D. W., Jr.: Chemical, Clinical, and Immunological Studies on the Products of Human Albumin Fractionation: VIII. Clinical Use of Concentrated Human Serum Albumin in Shock, and Comparison with Whole Blood and with Rapid Saline Infusion, J. Clin. Investigation **23**:491, 1944.

conditions of war concentrated albumin has many advantages. It is possible that the danger of hepatitis resulting from transfusion of blood and plasma can be avoided by using albumin.

SUMMARY AND CONCLUSIONS

1. Human albumin was given to 7 normal subjects and to 33 patients with circulatory failure. There were no unfavorable reactions.

2. In the normal subjects a rise in right atrial pressure and a fall in the hematocrit reading always occurred. The changes in cardiac output were variable. The arterial pressure and pulse rate usually remained unchanged.

3. In patients with hemorrhage, wounds of the chest, pericardial tamponade, burns, dehydration and infection, satisfactory hemodilution occurred when albumin was given in concentrated form (25 per cent solution).

4. The average increase in volume of blood for the entire group per gram of albumin administered was 14.0 cc. Dehydration was present in 4 of these patients, and the average increase per gram of albumin was 13.0 cc.

5. Eleven patients received 50 Gm. of albumin in fifteen minutes or less. The fact that these large quantities of protein can be given so rapidly makes concentrated albumin solution a valuable material to have on hand in the accident ward.

6. Human albumin is a useful substitute for plasma. It cannot replace the use of whole blood, but its small bulk, the ease and rapidity of its administration, its stability at room temperature and the absence of unfavorable reactions make it useful in many emergencies.

This work was done with the technical assistance of Mrs. Jane Bailey, Miss Eloise Cavin, Miss Maurine Giese and Miss Lois Jackson.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1945

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THE electrical examination of the nerve and muscle has long been an important part of the neurologist's work. Since the days of Erb the determination of the reaction of muscle to faradic and galvanic stimulation has been the common practice. This gave qualitative results of value to the clinician, but the importance of changes of polarity was overemphasized, and the "R.D." (reaction of degeneration) was at best a rough test of function. Since this, "chronaxie" has had its day and failed to satisfy the needs of a useful clinical test. It is now replaced by two methods: (*a*) the determination of strength-duration curves, i. e., the relation of voltage to duration in time of the stimulus,[1] and (*b*) the measurement of the accommodation constants of muscles during regeneration by progressively modulated currents.[2]

It now seems possible that the improved technics of electromyography may supplant these other electrical methods for clinical diagnosis. Records of the action potentials of human muscles have been used for clinical diagnosis since the pioneer work of Piper,[3] but his method of using a string galvanometer with leads to electrodes applied to the skin led only to a few clinical contributions. Tremors were well shown,[4] and those due to neurologic lesions were differentiated from hysterical tremors.[5] Recently leads from the skin over muscles have been used by Harvey and Kuffler[6] to record muscular action potentials on an electrocardiographic apparatus. By stimulating the appropriate nerve at a point higher on the limb, they recorded electrical potentials in normal and in partially paralyzed muscles, compared

1. Ritchie, A. E.: Electrical Diagnosis of Peripheral Nerve Injury, Brain **67**:314, 1944.

2. Pollock, L. J., and others: Electrodiagnosis by Means of Progressive Currents of Long Duration, Arch. Neurol. & Psychiat. **51**:147, (Feb.) 1944.

3. Piper, H.: Ueber den willkürlichen Muskeltetanus, Arch. f. d. ges. Physiol. **119**:301, 1907.

4. Salomonson, J. K. A. W.: Tonus and Reflexes, Brain **43**:369, 1921.

5. Cobb, S.: Electromyographic Studies of Muscles During Hysterical Contraction, Arch. Neurol. & Psychiat. **4**:8 (July) 1920.

6. Harvey, A. M., and Kuffler, S. W.: Motor Nerve Function with Lesions of Peripheral Nerves: Quantitative Study, Arch. Neurol. & Psychiat. **52**:317 (Oct.) 1944; Synchronization of Spontaneous Activity in Denervated Human Muscle, ibid. **52**:495 (Dec.) 1944.

the records and were able to measure the curves and give some quantitative idea of the return of function in such neural lesions as peripheral neuritis.

Fundamental work was made possible by the introduction by Adrian and Bronk [7] of the concentric needle electrodes that could be thrust through the skin into the muscles, where they could pick up potentials from single motor units or single muscle fibers. For years this method was used in physiologic research, but only recently was it taken over by clinical neurologists for the study of injuries to peripheral nerves and muscular weakness and atrophy. In Denmark Buchthal and Clemmesen [8] made beautiful electromyograms of different muscular affections, especially those causing atrophy. In this country Brazier, Watkins and Schwab [9] have studied the electromyographic changes in poliomyelitis, neural injuries and polyneuritis. These authors are especially careful in their terminology and define important terms as follows:

Fibrillation: the involuntary contraction (or the electrical potential resulting from the contraction) of a single muscle fiber. This fibrillation is only found in denervated muscle. Electrically it is a potential change of such short duration (one to two milliseconds) that it cannot be recorded by an inkwriting oscillograph. One needs a cathode ray oscilloscope to record it. Its voltage is rarely above 50 microvolts.

Fasciculation: the involuntary contractions of those muscle fibers served by one motor unit (i. e., the twitches seen by the neurologist in such diseases as amyotrophic lateral sclerosis and usually loosely described by him as "fibrillations"). These fasciculations are motor unit potentials and are of longer duration than fibrillations (e. g., five to ten milliseconds) and are therefore easily recordable with an inkwriting oscillograph. They may be of quite high voltage (500 microvolts).

Action potential: those potentials produced by voluntary action (i. e., contraction) of the muscle (never spontaneously occurring dis-

7. Adrian, E. D., and Bronk, D. B.: Discharge of Impulses in Motor Nerve Fibers: Frequency of Discharge in Reflex and Voluntary Contractions, J. Physiol. **67**:119, 1929.

8. Buchthal, F., and Clemmesen, S.: On the Differentiation of Palpable Muscle Affections by Electromyography, Acta med. Scandinav. **105**:48, 1940; On the Differentiation of Muscle Atrophy by Electromyography, Acta psychiat. et neurol. **16**:143, 1941.

9. Watkins, A. L.: Electromyographic Studies in Poliomyelitis, Journal-Lancet **64**:233, 1944. Brazier, M. A. B.; Watkins, A. L., and Schwab, R. S.: Electromyographic Studies of Muscle Dysfunction in Infectious Polyneuritis and Poliomyelitis, New England J. Med. **230**:185, 1944. Watkins, A. L., and Brazier, M. A. B.: Studies on Muscle Innervation in Poliomyelitis and Nerve Injuries, Arch. Phys. Med. **26**:69, 1945; Observations on Muscle Spasm in Poliomyelitis, ibid. **26**:325, 1945.

charges in a muscle at rest). In this Brazier and her colleagues differ with Weddell, who is confusing in the field of regenerating nerve, where two phenomena may be present together: (1) spontaneous fasciculations in the muscle at rest, denoting regrowth of some nerve fibers to that muscle, and (2) action potentials produced by voluntary attempts at contraction of the muscle, denoting either some remaining intact fibers or some completely regenerated ones already capable of function.

Weddell, Feinstein and Pattle [10] have published a comprehensive paper on "Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions." They somewhat modified Adrian's coaxial needles, using hypodermic needles of gages 20 to 26 and from ½ inch (1.27 cm.) to 3 inches (7.62 cm.) long. With these as pairs of electrodes in the muscles (the core being the one and the hollow shaft the other of the pair) the currents were led off to an oscillograph, and the results were either seen or recorded by the oscilloscope or heard over a loud-speaker, the latter being the most useful for diagnostic purposes.

Their preliminary work on normal muscles in man indicates that a motor unit in voluntary (striated) muscle consists of a single discrete group of contiguous muscle fibers innervated by one neuron. The average size of the discharge potential of a motor unit in a limb muscle is larger than in facial and laryngeal muscles; it is usually monophasic or diphasic, with a duration of five to ten milliseconds. The fibrillation potentials [11] of denervated muscle are shorter, sharper diphasic spikes of a duration of only one or two milliseconds and an amplitude of not more than 100 microvolts, whereas motor unit action potentials which occur in normal muscle or voluntary contraction may have an amplitude ten or twenty times greater. These small spikes recorded from denervated muscles are the fibrillation potentials studied by Denny-Brown and Pennybacker [12] in 1938. They believe that the fibrillation seen in muscles undergoing atrophy is due to rhythmic twitches of a single muscle fiber. These become sensitized by neural atrophy, and small amounts of acetylcholine circulating in the normal circulation set them off. The potentials obtained from fasciculating muscles in men suffering from amyotrophic lateral sclerosis and from traumatic section of nerves are unlike those shown by experimental animals with denervated muscle. When a denervated muscle has undergone

10. Weddell, G.; Feinstein, B., and Pattle, R. E.: Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions, Brain **67**: 178, 1944.

11. Weddell's use of the term "action potentials" for the fibrillations of denervated muscle seems to me misleading—for a completely denervated muscle is incapable of "action" on any voluntary basis.

12. Denny-Brown, D., and Pennybacker, J.: Fibrillation and Fasciculation in Involuntary Muscle, Brain **61**:311, 1938.

fibrosis, no fibrillation potentials can be obtained. The number and frequency of these potentials are increased by heat and neostigmine. Muscles that have long been splinted show little fibrillation, while those that have had adequate physical therapy are likely to fibrillate actively.

Totally denervated muscles can be distinguished from those with partial lesions of the nerve, the former showing only fibrillation spikes in the electromyograph and the latter mixtures of these with motor unit potentials. The relative amount of each gives an indication of the extent of nerve injury.

Particularly interesting are the observations on such common clinical conditions as "Saturday night paralysis," "crutch palsy" and "Bell's palsy." These are generally considered to be due to pressure on the nerve, but Denny-Brown and Brenner [13] have shown that it is not the pressure on the axons that stops conduction, but the pressure on vessels, causing ischemia of the nerve. Weddell and his colleagues combine such clinical conditions under the functional diagnosis "reversible ischemic block." With the electromyograph, "insertion" motor unit potentials can always be obtained in these cases on insertion of the needle, and it is usual to find few repetitive motor unit potentials which may or may not be under voluntary control. On the other hand, fibrillation potentials are few in number or absent. Such a picture gives a good prognosis for rapid recovery.

The time of change from motor unit potentials to fibrillation spikes in a denervated human muscle is variable. Roughly speaking all motor unit activity seems to be lost fifteen to twenty days after the neuronal lesion, while fibrillation spikes may begin to appear as early as the tenth day. The time needed for reinnervation of course depends on the location of the lesion. If the lesion is central (inside the dura) and if it is complete, no regeneration will occur. If the lesion is peripheral and the neural injury a clean cut with good surgical repair, the time of reinnervation depends on the distance of the neural injury from the muscle, the rate of growth of the axons being probably 1 or 2 mm. a day. When reinnervation begins in a muscle, the number of fibrillation spikes decreases in the electromyograph, and a few motor unit potentials appear in response to an effort to contract the muscle, as well as spontaneous motor unit potentials at rest. This is some days or weeks before the first contraction of the muscle can be seen clinically. The spontaneous motor unit potentials are small and polyphasic and are most numerous in the early stages of regeneration, but they may be found as long as eighteen months after reinnervation has begun. Experiments with neostigmine suggest that this drug facilitates neuromuscular transmission in early stage of reinnervation.

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13. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, Arch. Neurol. & Psychiat. **51**:1 (Jan.) 1944.

Weddell and his colleagues not only studied the many traumatic neural injuries of war, but also report on 37 cases of facial paralysis and show the usefulness of the electromyographic method in giving prognosis and indication for operation. They also discuss injury and disease of the spinal cord and show that electromyography can aid greatly in localizing the level of a lesion, in telling spinal from root lesions and in giving prognosis. In sciatica from prolapsed intervertebral disk the level of the lesion can sometimes be accurately determined by finding fibrillation spikes in the affected muscles. Watkins and Brazier [14] have used these technics successfully for locating the level of prolapsed vertebral disks in the cervical region.

In the course of this long and important paper Weddell and his colleagues take a fling at the vexed subject of "tonus." They recall that in 1931 Sherrington suggested that the word be dropped from the scientific vocabulary because of its vagueness and multiple meanings. Even when the term is applied to skeletal muscle it describes a complex mechanism under one heading and gives a false impression, unless it is clearly understood that the clinician means nothing more than "the constant slight tension characteristic of healthy muscle, which offers a steadily maintained resistance to stretching." [15] This is a difficult thing to test clinically and diagnoses based on it are not very dependable even when the observations are made by experienced neurologists. Weddell's contribution to the subject is his observation that when a muscle is completely relaxed there are no potentials recorded by electromyography. He illustrates our understanding of muscle "tone" by enumerating the following factors that go to make for muscular resistance to passive stretch: (1) the amount of extravascular fluid in the muscle, (2) the degree of congestion of the muscle (intravascular fluid), (3) tightness of the fascia and mechanical elastic factors and (4) motor unit activity set off by stimuli from the nervous system.

The fourth factor is the one about which neurologists usually think without considering the other three, and Weddell's point is well taken that all must be considered. His discussion of the neurologic mechanism is confused by bringing in "the emotional, or conscious level" (which is not defined). As long as this supernatural ingredient is left in, the term "tonus" will stick. Weddell does not make it clear that the neurologic part of "tone" is simply reflex postural contraction from the various levels of the central nervous system. When this nervous mechanism is active, as it is in many muscles most of the time, potentials are recordable by the electromyograph.

14. Brazier, M. A. B.; Watkins, A. L., and Michelsen, J. J.: Electromyography in the Differential Diagnosis of Cervical Ruptured Disk, Arch. Neurol. & Psychiat; to be published.

15. Holmes, G.: Cerebellum of Man, Brain **62**:1, 1939.

No explanation of the electrical phenomena of muscle as seen in the electromyogram will be valid until more is known about the mechanism of muscular contractions. A great step in advance seems to have been made by Szent-Györgyi and his collaborators. Their work is summed up in a monograph entitled "Studies on Muscle."[16] Their studies on myosin threads and insect muscles have led them to picture the model of striated muscle as made up of long actin threads with myosin micelles attached to them and winding about them in a spiral fashion. The first change, when contraction occurs, is a change in ionic distribution which discloses itself in an electrical potential and contraction in volume. The contraction of actomyosin is fast and extensive because the fiber is an asymmetric system of which one half (the myosin) shrinks rapidly and causes the fiber to curl and contract in spirals, shortening and thickening the whole muscle mass.

THE MOTOR AREAS OF THE CEREBRAL CORTEX

The localization of function in the cortex of the brain has long been a field of productive investigation by physiologists and clinical neurologists. The admirable monograph on "The Precentral Mortor Cortex" from the University of Illinois, edited by Paul Bucy, presents a mass of important data but shows how little is really known about the functions of the brain.[17] Here are 605 pages devoted to a study of the motor area, the part of the cortex longest known and most accurately studied, and yet many important points are still unsettled about the cortical fields and their projections on lower neuronal levels. Chapter 2, by von Bonin, describes the cellular architecture of the precentral areas. Taken as a whole, this subsector of the cortex is the one that receives thalamocortical fibers from the ventrolateral nucleus of the thalamus, relayed from the dentate nucleus. In general he accepts the old Brodmann scheme for areas 4, 6 and 44 (fig. 1). Area 4 lies in and closely anterior to the fissure of Rolando (central sulcus) but is divided now by von Bonin into three subdivisions: 4 gamma, 4a and 4s. Area 4 gamma contains the giant motor cells of Betz. Area 4a is similar in structure to 4 gamma, but has no Betz cells. Area 4s has large motor cells in the fourth layer, not giant cells in the fifth layer as in area 4 gamma.

The pyramidal tract, i.e., that bundle of fibers that makes up the "pyramids" of the medulla oblongata, is not entirely understood. Only about one third of its constituent fibers come from the giant cells of Betz in the motor cortex. The origin of the other two thirds is still a

16. Szent-Györgyi, A.: Studies on Muscle, Acta physiol. Scandinav., 1945, supp. 25.

17. Bucy, P. C.: The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol 4, nos. 1-4, p. 605.

matter for discussion. One thing can be emphatically stated, and that is that the old schematization of the motor mechanism into an "upper motor neuron" and a "lower motor neuron" is an oversimplification that is inaccurate and misleading, both physiologically and anatomically. Even in the pyramidal tract there are usually internuncial neurons between the corticospinal fibers and the ventral horn cells. In the extrapyramidal systems there are many of them. In fact, the extrapyramidal tracts are characteristically composed of series of neurons that only after several relays reach the ventral horn cells to discharge on the "final common path" to the muscle. Levin, who writes the chapter on "Efferent Fibers" in this monograph, describes three main motor projections from the precentral areas: first, the corticospinal tract, which rises exclusively from the motor area proper (area 4); second,

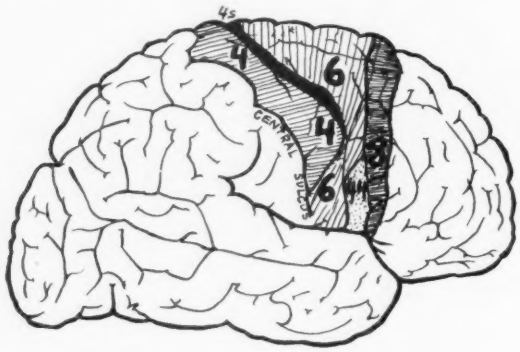

Fig. 1.—Brodmann's areas.

the corticonigral tract, from all parts of the precentral cortex (areas 6, 8, 4s and 4) to the substantia nigra in the brain stem, and third, the corticopontile tract, from all the motor areas to the nuclei of the pons. He states that small numbers of fibers pass from cortex to striatum, thalamus, zona incerta and red nucleus.

Kennard, in chapter 9, reproduces a diagram that shows direct fibers from areas 8 and 4s to the caudate nucleus, from areas 6 and 4 to the putamen and from 6 to the pallidum. Hines, in chapter 18, says that the origin of the tract from the frontal cortex to the pallidum is unknown, and that all areas of the motor cortex are related to each one of the main motor masses of the brain stem, except the corpus striatum. The function of the part of the pyramidal tract that arises in area 4 (according to Tower, who writes the chapter on "The Pyramidal Tract") is "somatotopically organized control of discrete movements," the extrapyramidal activity is on "a larger scale of distribution." What all this

signifies from the clinical standpoint is well expressed in a paragraph by Tower:

> As has been pointed out before, the lesions in man which produce the usual hemiplegia, or spastic paralysis, whether they lie in the cerebral cortex, internal capsule, or cord, are inevitably mixed pyramidal and extrapyramidal lesions, destroying fiber systems in both categories. And the symptomatology might be expected to be correspondingly compounded. The pyramidal elements in the total are easily recognized: loss of discrete control of the skeletal musculature, muscular atrophy, impaired or abolished superficial reflexes, and the sign of Babinski. But the muscular contractures, tonic neck reflexes, and the phenomena of spasticity are additional disorders, the consequences of extrapyramidal destruction.

From the normal physiologic viewpoint, Tower states that the pyramidal tract acts in two phases: There is a steady "tonic" innervation through all the waking hours which is a continual contribution to the central excitatory state of the spinal motor mechanisms, keeping them in readiness for the second of "phasic" activity which is episodic and appears as a specific contribution to individual motor acts.

In spite of differences in opinion concerning tracts and connections, the general consensus seems to be that area 4 has to do with discrete, learned movements ("pyramidal function"), and that areas 8 and 4s are "suppressor" in function. Area 6 is the main source of "extrapyramidal" fibers; it lies between 8 and 4s and is bounded below by area 44. Stimulation of area 6 gives rise to sustained contraction and complex progressive and rhythmic movements; the threshhold of area 6 is higher than that of area 4. All the areas, including 4, have extrapyramidal connections and functions. Area 44 subserves the delicate motor function of speech; lesions here may cause either dysarthria or apraxia, motor aphasia being synonymous with apraxia of the muscles of speech.

McCulloch's discussion in chapter 8 of the cortical connections as found by "physiological neuronography" is a fine piece of work that complements the anatomic studies and brings out connections not yet discovered by anatomic means. The author used the method of Dusser de Barenne, in which strychninization of the neural cells to be explored caused impulses to be set up which fired off electrical disturbances in the structure where the axon terminated. By picking up these characteristic potentials through an oscillograph the physiologic connections of one area with another were determined. O'Leary discusses in another chapter the relations between the form of the electroencephalogram and the anatomy of the cerebral structure. This is a good beginning in a difficult field.

More from the clinical standpoint Erickson discusses electrical stimulation of the cortex in man at operation, giving maps of the human

cortex with stimulable points. He mentions that the first stimulation was done by Robert Bartholow of Cincinnati in 1874. Bucy has two important chapters, one on extirpation in man and the other on the relation of the motor cortex to abnormal involuntary movements. Both are careful presentations of the data. In the latter the conclusions as to the sources of athetoid movements and of tremor are of necessity somewhat speculative. His theory of parkinsonian tremor is that such a tremor may develop because of interruption of a circular controlling mechanism which passes from the precentral motor cortex to the substantia nigra, globus pallidus, thalamus and thence back to the cortex. He mentions my theory [18] as an alternative. There seems to me to be no antagonism between our theories. I described the various extrapyramidal pathways between cortex and cord and postulated that partial interruption of internuncial neurons caused a disturbance in the normal asynchronous extrapyramidal impulses, leaving the field clear for a synchronous rhythmic discharge which caused tremor. Bucy's scheme of an interruption of a "circular controlling mechanism" might act in the same way.

Marion Hines writes the last chapter of the volume, giving a thoughtful and carefully worded exposition of the "Significance of the Precentral Motor Cortex." She differs from some of the other investigators by saying that there are no fibers from areas 6 to area 4 and no projection fibers from any part of the "precentral subsector" to the striatum. In her discussion of stimulation experiments she expresses the view that single muscles can be stimulated from points in area 4, but holds that this does not demonstrate the ability of that region to produce movement per se, that it only demonstrates what a certain electrical current can do. She believes that the sine wave current gives the best results. Muscles may be represented in more than one point and at one point more than one muscle may be made to contract, but one muscle is predominantly represented. Moving forward from area 4 (using the sine wave current at threshhold), the isolated focal movements are lost and more synergic movements appear, i.e., the extrapyramidal type. Hines points out that many otherwise good investigations of motor function have lost much by not describing muscular movements in an orderly and objective fashion. According to her a skilled act is performed by: (*a*) the discrete movements of intact musculature, called the prime mover, (*b*) cooperating movements of more proximal muscles, (*c*) fixation and holding contractions at the girdle and (*d*) contractions of antagonistic muscles. These factors may be seen clinically in normal and pathologic movements and may be produced to some extent as isolated phenomena in stimulation experiments.

18. Benda, C. E., and Cobb, S.: On the Pathogenesis of Paralysis Agitans, Medicine **21**:95, 1942.

It seems to me that the much argued question as to whether the "motor cortex innervated muscles or movements" has not yet been answered. The evidence strongly suggests, however, that the normal function of the motor cortex always has to do with movements, although artificial means of stimulation of area 4 can elicit contractions of single muscles or even parts of muscles.

Removal of a part of the motor areas causes more or less loss of function, i.e., paralysis or paresis. There is in addition a release of function causing the phenomena of "hypertonus, clonus, brisk and irradiating tendon reflexes and associated movements." Cutting the tracts in the pyramids of the medulla causes loss of only one of these, the associated movements. This is what one would expect, because the other "release phenomena" seem to be extrapyramidal functions and interruption of pathways would have to be at a high level, since "release" can only be explained if some of the large motor nuclei of the base of the brain are released from above.

Finally Hines sums up the function of the motor cortex in three remarkable paragraphs, as follows:

> In conclusion, the significance of the precentral motor cortex lies in its ability to confer upon the individual who possesses it within an intact nervous system, choice of initiation of contraction of single muscles or their functional units. This initiation of contraction is accompanied by that of cooperating muscles, by fixation of more proximally lying muscles, and by graded contraction or relaxation of antagonists. In skilled performance directed to accomplish a given end, the "fusillade" innervation of the cooperating extremity is as important as the innervation of the active or leading extremity. This cortical tissue makes possible stopping a movement at a given degree of contraction, and starting it again at a degree of contraction necessary to follow through to the desired end easily and without effort. Stereotyped patterned movements, integrated at lower levels, can be utilized as parts or wholes. Postural patterns can be assumed, modified and shifted such that an undetermined move can be made easily and instantly. To be "on his toes" is more than a trite expression.
>
> Posture must not only be maintained in an easy, natural way to free the hand for manipulation, but must also anticipate by its adjustments that next movement. Exquisite as the movements of the fingers are, they do not work alone. And the variants in cooperation of movement, in fixation and in the increment and decrement of tone of muscles of the trunk, of those which attach the extremities to the girdles, and of those of the proximal part of the extremities are as important as movements of the digits in the attainment of skilled movements. No violin or piano was ever played with the fingers and hand alone.
>
> The precentral motor cortex is not an isolated piece of nervous tissue sending out its impulses to lower motor centers. Its accomplishments are dependent upon the intactness of its thalamocortical relations. The instant obedience of muscles demanded in the performance of skilled movements is dependent upon intactness of other parts of the nervous system, in particular that of the basal ganglia and the cerebellum. The nice modulation of movement requires relation of this tissue to other cortical areas. The precentral motor cortex reaches out to constrain cooperation of its mirrored counterpart; it requests the contribution of the post-

central gyrus via fibers which run beneath its posterior boundary. It receives modifying impulses from all the somaesthetic sectors of the parietal lobe.

Taken as a whole this monograph, written by fifteen leaders in the field in eighteen chapters, is a great reference book for source material, but it leaves the reader with a certain confusion regarding disputed facts of observation and moot points of theory. The subject is complex and difficult even though it concerns the simplest and best known part of the cortex. It is therefore with thankfulness that one turns to the short paper by Welch and Kennard on the "Relation of Cerebral Cortex to Spasticity and Flaccidity," [19] where a theoretic explanation is given briefly with a clarifying diagram. The authors state:

> Certain preliminary observations on spasticity and flaccidity following removal of various areas of the sensorimotor cortex in monkeys led to the present investigation. These were (i) although removal of area 6 caused spastic paresis and removal of area 4, flaccidity, simultaneous removal of both areas produced greater spasticity than did excision of area 6 alone; (ii) primary removal of the postcentral gyrus caused flaccidity with minimal paresis; (iii) removal of an entire hemisphere caused more marked spasticity and paresis than did removal of the motor and premotor areas alone. . . .
>
> It has also been established that primary injury to area 6 results in reflex grasping and slight increase of resistance to passive flexion and extension. If area 4s, lying between areas 4 and 6, is destroyed, alone or in combination with area 4 or area 6, spasticity results. Furthermore, lesions to area 6 intensify ipsilateral spasticity and bilateral removal of areas 4 and 6 results in great paresis and spasticity in all extremities.

The experiments performed by Welch and Kennard showed that in monkeys and chimpanzees removal of area 6, including 4s, was followed by moderate spastic paresis; removal of area 4 (excluding 4s) was followed by paresis without spasticity. Combinations of 4, 4s and 6 caused more spasticity; lesions of 4 combined with postcentral ablation caused some spasticity. These data are summed up in their figure 3 (here reproduced as fig. 2). The pyramidal fibers (represented as block pyramids with axons projecting downward) act directly on the motor cells of the cord at or near the final common pathway to direct fine volitional movements. The extrapyramidal fibers (represented by black circles with axons) act on subcortical nuclei integrating postural and locomotor adjustments. When the predominantly pyramidal areas are removed, there is paresis with little or no increased resistance to passive manipulation; when the areas are largely extrapyramidal, there is spasticity. Combinations of lesions add to the spasticity because more extrapyramidal neurons are injured. In terms of the diagram, the more black pyramids injured, the more paresis; the more black circles injured,

19. Welch, W. K., and Kennard, M. A.: Relation of Cerebral Cortex to Spasticity and Flaccidity, J. Neurophysiol. **7**:255, 1944.

the more spasticity, because removal of the circles releases the extrapyramidal motor nuclei.

Lassek,[20] who has written several papers on the pyramidal tract, believes that general suppression of cerebral activity causes the Babinski phenomenon and that local pyramidal inhibition could do the same. This would correspond to the theory that the Babinski sign is caused by loss of pyramids, as in Welch and Kennard's diagram, a satisfactory theory for the present.

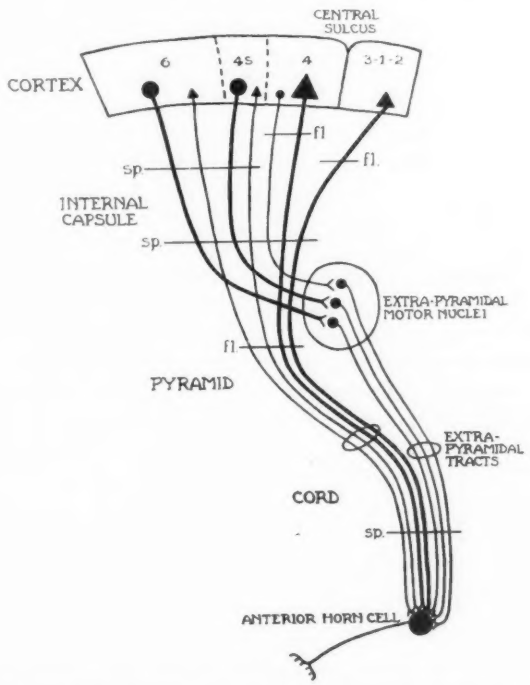

Fig. 2.—Diagram of pyramidal and extrapyramidal pathways. (From the *Journal of Neuropsychiatry*, **7**:255, 1944, by permission of Charles C Thomas, Publisher.)

CONCUSSION OF THE BRAIN

In warfare since the Stone Age and in civil life since the advent of the automobile, cerebral concussion has been a great medical problem.

20. Lassek, A. M.: Human Pyramidal Tract: XI. Correlation of the Babinski Sign and the Pyramidal Syndrome, Arch. Neurol. & Psychiat. **53**:375 (May) 1945.

What is it that "knocks a man out" so quickly and completely, often with little or no subsequent disturbance? Three recent papers, two by Walker and his colleagues [21] and the other by Denny-Brown,[22] throw new light on the subject and decribe mechanisms which have physiologic meaning to replace the old vague theories of vascular paralysis, waves of fluid pressure, molecular shock and synaptic dysfunction.

The best clinical definition is that of Trotter [23]: "An essentially transient state due to head injury which is of instantaneous onset, manifests widespread symptoms of purely paralytic kind, does not as such comprise any evidence of structural cerebral injury, and is always followed by amnesia for the actual moment of the accident." The instantaneousness and transitory nature are here emphasized, which distinguish the condition from cerebral contusion, which may result from slow pressure, without loss of consciousness, although the pathologic lesions of contusion and laceration may sometimes accompany concussion. The subject under discussion here, however, is concussion that shows no gross or microscopic lesions of the brain at autopsy a few hours after the accident. This proviso as to time is made because Windle, Groat and Fox [24] have observed chromatolysis of nerve cells beginning fourteen hours after concussion and progressing to the sixth or eighth day. These changes are probably largely reversible, but some nerve cells may be destroyed.

Denny-Brown emphasizes that concussion occurs when the head is thrown suddenly and violently into motion or is suddenly stopped when in motion. He speaks of this as "acceleration concussion" and shows by his experience on animals that it occurs regularly when a pendulum at a velocity of 28 feet a second strikes a movable head. Calculations of the impacts that caused traumatic amnesia in man show that the velocity was 24 feet per second or greater, so that the critical speed of acceleration or deceleration is probably something of this order of magnitude.

When this kind of concussion occurs, the experiments show that there is a sudden brief rise of intracranial pressure with condensation of the substance of the brain. It is this sudden physical condensation of nervous tissue which is important. Electroencephalograms show that there is a short explosion of potentials of high voltage followed by a

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21. (*a*) Walker, A. E.: Syndrome of Cerebral Concussion, Clinics **4**:361, 1945. (*b*) Walker, A. E.; Kollros, J. J., and Case, T. J.: Physiological Basis of Concussion, Physiol. Rev. **25**:296, 1945.

22. Denny-Brown, D.: Cerebral Concussion, Physiol. Rev. **25**:296, 1945.

23. Trotter, W.: Certain Minor Injuries of the Brain, Lancet **1**:935, 1924.

24. Windle, W. F.; Groat, R. A., and Fox, C. A.: Experimental Structural Alterations in the Brain During and After Concussion, Surg., Gynec. & Obst. **79**:561, 1944.

prolonged period of decreased electrical activity and raised threshhold to all stimuli. In other words, there is a sudden intense period of widespread nervous excitation followed by lack of response. The clinician might correlate these with the "seeing stars" and the following paralysis and amnesia. That the stimulus and following inactivity are widespread in the central nervous system is shown by the clinical observation of paralysis affecting all levels from the higher "conscious" mechanisms to the vegetative levels expressed in dilated pupils, apnea and vasoconstriction. The electroencephalograph shows that the cerebrum is widely affected, and Denny-Brown's observation that concussion can occur in decerebrate animals proves that lower centers are also involved.

Walker and his co-workers [21b] do not believe that acceleration is an essential factor, and emphasize that concussion is a direct mechanical and widespread effect on nerve cells causing excitation and discharge. Their ingenious and beautifully executed electroencephalographic experiments support this contention. To me the argument as to whether the phenomena of concussion are "excitatory" or "paralytic," or due to "acceleration" or "compression" seems largely semantic. The point is that commotio cerebri has been taken from the realm of speculation and given by all these investigators a specific physical and physiologic basis. When more is known about the nature of the nerve impulse and electrons, the process of concussion may be expressed in terms of polarized cell membranes and positive and negative charges, but that time is still far ahead.

PSYCHOPATHIC PERSONALITY AND EPILEPSY

"Experience in the war has demonstrated very clearly that incorporation in a disciplined force with rigid standards will often exhibit inadequate and aggressive individuals as sociopathic failures or delinquents." This quotation from Curran and Mallinson's review [25] of the "Psychopathic Personality" brings up a problem which has been of great importance in the armed forces. Although much less is written about them, some statistics show [26] that "psychopaths" were more common than "neurotics" in the military hospitals and training centers.

The misuse of the term "psychopathic personality" by persons not trained in psychiatry is a great difficulty, because to most people and

25. Curran, D., and Mallinson, P.: Recent Progress in Psychiatry: Psychopathic Personality, J. Ment. Sc. **90**:266, 1944.

26. Hall, R. W.: Peculiar Personalities, War Med. **1**:383 (May) 1941. Wittson, C. L.; Harris, H. I.; Hunt, W. A., and Solomon, P.: Neuropsychiatric Examination of Recruits at the United States Naval Training Station, Newport, R. I., War Med. **2**:944 (Nov.) 1942.

to many physicians the term signifies anybody who is mentally abnormal, no matter what the diagnosis. Prue [27] says:

> The unsatisfactory state of the concept of psychopathic personality illustrates the futility of orienting psychiatric research about the traditional clinical entities as "diseases" of nineteenth century psychiatry. What is needed is a clear description of various problems of behavior expressed in simple unambiguous language. It would thus be possible to undertake a common sense attempt to specify the etiologic factors without preconceived bias. Having done this, one could approach the problems of prevention and treatment in a logical, systematic fashion.

Many psychiatrists, however, use the term "psychopathic" in a quite definite way. There are two main types, the inadequate and the aggressive. Both are fundamentally unreliable; "the truth is not in them." In spite of good intelligence they do not seem to be able to look ahead and realize the probable results of their acts. They live largely for the moment, and are plausible, talkative and often very beguiling at the beginning of an acquaintance, but they are disappointing and in the end "let their friends down" by lying, stealing and fugitive behavior. They are the "rolling stones" of literature, the "moral imbeciles" of an earlier psychiatric nomenclature. Many take to alcohol, many have unorthodox sex habits and most get into the hands of the police. None of them hold a job long. They are tramps, bums, hoboes, confidence men, men about town and occasionally, like Wilson Mizner,[28] earn much money and spend it lavishly.

It is no wonder that people of this sort when put into a permanent, disciplined situation like the army find themselves continually at odds with authority. Like Kipling's "Tramp Royal" they must restlessly move on:

> Speakin' in general, I 'ave tried 'em all—
> The 'appy roads that take you o'er the world.
> Speakin' in general I 'ave found them good
> For such as cannot use one bed too long,
> But must get 'ence the same as I'ave done,
> An' go observin' matters till they die.

Responsibility, security and routine are to them anathema.

The older theory was that they were "constitutional psychopathic inferiors," born that way with bad genes. More recently some psychiatrists have looked on them as "neurotic characters," and psychoanalysis has been futilely tried to reorganize their personalities. Now evidence is coming to the fore that many of them are victims of cerebral injury, including trauma, inflammation or agenesis, and show abnormal electro-

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27. Prue, P. W.: Concept of Psychopathic Personality, in Hunt, J. McV.: Personality and the Behavior Disorders, New York, The Ronald Press Co., 1944, p. 922.

28. Johnston, A.: Legend of a Sport, The New Yorker, Oct. 10, 1942, p. 21.

encephalograms.[29] It has been long known that the postencephalitic "problem child" frequently had an abnormal electroencephalogram and that the line between such children and epileptic persons was difficult if not impossible to draw. It now seems possible that many patients with the diagnosis of psychopathic personality are to be looked on as similar to some adults with epilepsy, whose sudden fugues might be considered exaggerations of the unpredictable behavior of the psychopath. In a few cases phenobarbital and diphenylhydantoin sodium have been of use in checking the psychopathic behavior. Doubtless many of these patients inherit inferior brains and are hopeless from the standpoint of therapy, and some may have defects in character of a psychogenic (environmental) origin. Recent opinion stresses the importance of etiologic diagnosis and management by institutionalization, social adjustment and drugs.

Lennox [30] has just published two papers dealing with the successful use of 3, 5, 5-trimethyloxazoladine-2, 4-dione, which is manufactured by the Abbott Laboratories under the trade name of Tridione. He says the drug is effective in controlling or greatly diminishing attacks of petit mal, myoclonic epilepsy or akinetic seizures. It is of no benefit in cases in which the seizures are mainly of the grand mal convulsive type. From the electroencephalographic standpoint it seems to do most good to the patients who show abnormality of the dome and spike type. The only untoward effect so far noticed is photophobia.

29. Gottlieb, J. S.; Knott, J. R., and Ashby, M. C.: Electroencephalographic Evaluation of Primary Behavior Disorders in Children, Arch. Neurol. & Psychiat. **53**:138 (Feb.) 1945. Silverman, D.: Electroencephalogram of Criminals, ibid. **52**:38 (July) 1944. Knott, J. R., and Gottlieb, J. S.: Electroencephalographic Evaluation of Psychopathic Personality, ibid. **52**:515 (Dec.) 1944.

30. Lennox, W. G.: Epilepsy, Clinics **4**:504, 1945; Petit Mal, Myoclonic and Akinetic Epilepsies and Their Treatment with Tridione, J. A. M. A. **129**:1069 (Dec.) 1945.

Book Reviews

Pulmonary Tuberculosis in the Adult. By Dr. Max Pinner. Price, $7.50. Pp. 579. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Dr. Pinner modestly states in his preface that this book is not a textbook and that the primary aim "is not to impart knowledge but to create understanding." None the less there is little of importance about pulmonary tuberculosis which is left unsaid in this interesting treatise by a man who has thought long and carefully on the subject. One of the valuable features is the thorough lists of references, which follow each chapter. The author uses the device of inserting after each title a short paragraph in which the substance of the article is abstracted. There are numerous excellent illustrations and indexes.

A Primer of Electrocardiography. New Edition. By G. E. Burch, M.D., and T. Winsor, M.D. Price, $3.50. Pp. 215. Philadelphia: Lea & Febiger, 1945.

A primer is either an elementary schoolbook or a brief introduction to any subject. It should be short, clearly written and interesting.

This primer of electrocardiography meets these requirements. It has been constructed mainly for students and as a supplement to the more elaborate texts on electrocardiography, which are now so numerous that every medical school library has several on hand. Its charm lies in its simplicity: The language is clear and not too technical or wordy; the illustrations are diagrammatic and easily interpreted, and the arguments are stated with the assurance and positiveness that students always like.

On the whole, this small book deserves considerable popularity. It is certain to make many friends.

Pediatric X-Ray Diagnosis. By John Caffey, M.D. Price, $12.50. Pp. 860, with 711 illustrations. Chicago: The Year Book Publishers, Inc., 1945.

This is an expensive book, printed in large type on smooth paper, so that it appears especially well dressed and stylish. What it has to say is clear and to the point, and the illustrations are admirable. There seem to be enough differences between the roentgenologic observations on infants and those on persons in later life to make such a volume useful. It describes especially well the congenital defects and the diseases of bone with which internists—and radiologists, too, for that matter—who work with adults have little acquaintance. It is an excellent work of reference and deserves high praise.

Pathology of Tropical Diseases: An Atlas. By J. E. Ash, M.D., and Sophie Spitz, M.D. Price, $8. Pp. 350, with 941 illustrations, 15 in color, on 257 plates. Philadelphia: W. B. Saunders Company, 1945.

Colonel Ash and his colleagues have done a noteworthy service to American medicine by producing this atlas of the pathology of tropical disease, since, as far as the reviewer knows, nothing approaching it in usefulness is readily available at a reasonable price. Short but authoritative discussions of the various diseases are followed by the plates, which include maps, photographs of patients, reproductions of roentgenograms and photographs of gross specimens and histologic sections. The reproductions are excellent, and the microscopic sections, many in color and of high magnification, really show what the reader wants to know. The diagrams of the life cycle of parasites are unexcelled. The book is well got up on fine paper, and there is an index. It is hard to restrict one's praise of this excellent compendium.

Clinical Parasitology. By Charles Franklin Craig, M.D., and Ernest Carroll Faust, Ph.D. Fourth edition. Price, $10. Pp. 871, with 305 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1945.

This book has long held such an outstanding position that little need be said beyond reemphasizing some of its excellent features. These include good paper and print, numerous illustrations (some in color), diagrams, maps, index both by names and by subjects and thorough bibliography. As the authors point out in their preface, the volume has been completely revised and several new chapters have been added. The material is conveniently arranged, and the text is written with the obvious authoritativeness of those who have worked long in the field.

The Fundamentals of Electrocardiographic Interpretation. Second edition. By J. B. Carter, M.D., Assistant Professor of Medicine, Illinois College of Medicine. Price, $6. Pp. xvii + 406, with 307 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Every year the ARCHIVES is likely to review at least two or three books dealing with electrocardiography. Each review is likely to be worded in much the same manner, emphasizing the author's wish to produce something of practical aid to the medical student or to the clinician. Each book on the subject that is reviewed is likely to follow much the same pattern: some sort of an historical account of the electrocardiograph, some account of the technical use of the instrument and a variety of neatly interpreted tracings.

THE ARCHIVES reviewed the first edition of this book (**62**:1096 [Dec.] 1938). It concluded by predicting that the book without doubt would be helpful to the student, although the book embodied nothing that gave it any advantage over hitherto published books on the subject. The new edition is longer than the first, contains more illustrations and is $1.50 more expensive to purchase. What was said of the first edition holds true for the second.

Essentials of Clinical Allergy. By Samuel J. Taub, M.D. Price, $3. Pp. 198. Baltimore: Williams & Wilkins, 1945.

This monograph is written intelligently by a clinician who is familiar not only with allergy but also with medical students and practitioners. It discusses allergy from several viewpoints, laying especial emphasis on those kinds of allergy which appear most commonly in clinical work. Thus the author has a great deal to say about asthma and hay fever but comparatively little about gastrointestinal allergy or migraine or arthritis. He gives an excellent account of the detective work needed to track down the cause in any given case and sensible advice in regard to treatment.

On the whole, the volume promises well to fulfil the purpose for which it was prepared: to make the field of allergy easily accessible to beginners or to physicians who cannot possibly read their way through the maze of literature on allergy. It deserves success.

Pulmonary Tuberculosis: A Handbook for Students and Practitioners. By R. Y. Keers and B. G. Rigden, with a Foreword by F. H. Young. Price, $5. Pp. 273, with 124 illustrations. Baltimore: Williams & Wilkins Company, 1945.

This little book presents an admirable systematic discussion of pulmonary tuberculosis. As the authors say in their preface, they have tried to present "the position of pulmonary tuberculosis today, incorporating the advances in diagnosis and treatment which have occurred in the last two decades." The discussion of collapse therapy in its various phases seems especially sane and well tempered. There is a large number of excellent reproductions of roentgenograms. The style is clear and precise. There is an index.

Bronchial Asthma. By Leon Unger, M.D. Price, $9.00. Pp. 730 +, XVI. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

This volume of 730 pages on bronchial asthma by Dr. Unger is unique if for no other reason than that one man was able to fill so many pages on this subject. There is little doubt but that this large volume is the most complete thus far available on asthma. Certain important considerations, however, are either lightly passed over or erroneously presented. In discussing a disease process as severe as asthma, one should surely devote more than 8 pages to the disturbed physiologic factors, the understanding of which is so important if one is to treat the patient in a rational manner. The same criticism also applies to the cursory handling of the complication. The statement on page 323 that digitalis is of little value in the treatment of cardiac asthma is not substantiated by modern medical thought.

In general, the chapters on the allergic and the nonallergic treatment are well handled, although one is astonished that a man of such wide experience as the author would advocate cutting the ragweeds on empty city lots to decrease the incidence of asthma.

There are many good illustrations, particularly those dealing with pathology. However, some, such as figures 83 *A* and *B* and 86 fail to indicate what the author wishes to show. One might also draw attention to the lack of uniformity in reproducing roentgenograms; that is, figure 6 *A* is viewed in the anteroposterior position, while figure 67 is viewed in the posteroanterior position.

Of real value is the chapter on the contents of various patent medicines used in the treatment of asthma.

Government in Public Health. By Harry S. Mustard, M.D. Price, $1.50. Pp. 219. New York: Commonwealth Fund, 1945.

This handy book, written in not too technical language, presents an admirable survey of what public health is all about. The discussion of the historical development of public health measures in the United States is particularly valuable, and the division into chapters on federal, state and local health services simplifies an obviously complicated subject.

This treatise, the prospective reader should know, is sponsored by the Committee on Medicine and the Changing Order of the New York Academy of Medicine. It is one of a series of studies which, it is hoped, will help to orient those who see the need of progress in the various domains of medicine. It is to be hoped that this excellent study on government in public health, which emphasizes what has been achieved, will point out by implication some of the things which still need badly to be done.

Classic Descriptions of Disease. By Ralph H. Major, M.D. Third Edition. Price, $6.50. Pp. 727, with 137 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1944.

We already have reviewed the two previous editions of this book favorably (**50**:960 [Dec.] 1932 and **65**:1299-1300 [June] 1940).

The third edition is built on the lines of the first but is a little bigger, more profusely illustrated, and more expensive. There are included a few more classic descriptions of disease than appeared in the other editions, and now each new one is indeed a rarity, for all the familiar ones were long since used up. The short sketch of each writer which accompanies his classic description is sharply drawn, attempting only to reveal salient features; thus it avoids tedium.

An interesting innovation is the introduction of a bibliography, which is placed ahead of the index. Here one can find references to the best biographies that have been written about any of the contributors whose work is mentioned; this is an important and worth while improvement.

Clearly, we approve of this book. We repeat: It makes a fine addition to any library.

Annual Review of Physiology. Edited by James Murray Luck. Price, $5. Pp. 774 and vii. Stanford University, Calif.: American Physiological Society and Annual Reviews, Inc., 1945.

Like the previous "Annual Reviews of Physiology," this volume for 1944 is very good. The subjects covered are reviewed well. Such a review affords an opportunity for those who cannot follow the work in the physiologic literature to learn the important contributions made in the field. It also makes possible an opportunity for those in physiologic work to observe the data collected from many sources collectively, thus permitting a better evaluation. The complete bibliographies appended to each chapter serve as excellent references. Such a review is of great value to every worker in both the clinical and the preclinical medical sciences. It is recommended highly to all medical students, interns and residents, as well as to practicing physicians, who tend to neglect the problem of applied physiology.

Essentials of Body Mechanics in Health and Disease. By Joel E. Goldthwait, M.D.; Lloyd T. Brown, M.D.; Loring T. Swaim, M.D.; John G. Kuhns, M.D., and William J. Kerr, M.D. Fourth edition. Price, $5. Pp. 316, with 128 illustrations. Philadelphia: J. B. Lippincott Company, 1945.

This book, well printed and profusely illustrated with photographs, charts and diagrams, is the collaborative effort of acknowledged leaders in the field of orthopedics and body mechanics. The impact of abnormal posture and body mechanics on the various viscera and the diseases or disorders which may result are fully dealt with. Therapy is discussed in detail. There is an extensive bibliography. This book should be highly useful to the general practitioner in orienting him in a difficult field.

Textbook of Neuropathology. By Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School. Second edition. Price, $5.50. Pp. 370, with 289 illustrations. New York: Grune & Stratton, Inc., 1945.

The first edition of this book appeared in 1933. *The Journal of the American Medical Association* (**101**:1262 [Oct. 14] 1933) reviewed it favorably, saying that it was to be heartily recommended as an authoritative introduction to the subject.

The second edition is modeled on the first but carries forward the knowledge of the central nervous system a new ten years. It continues to discuss the pathology of the nervous system from a broad biologic standpoint, and by necessity is largely a text of histopathology. The first edition was printed by Lea & Febiger. The printers of the second edition use type that is somewhat different; the format, illustrations and tables are good. On the whole, the second edition deserves the same comment that was given to the first: It can be heartily recommended as an authoritative introduction to its subject.

Treatment in General Practice. By Harry Beckman, M.D. Fifth Edition. Price, $10. Pp. 1070. Philadelphia and London: W. B. Saunders Company, 1945.

This book has enjoyed the distinction of being the most popular one volume work on treatment since its first appearance in 1930. The author has periodically published new editions to keep the data abreast with the developments in therapy. This, the fifth edition, includes the newer advances in therapy. Clinical states which have become particularly important since the war, such as blast syndrome, chemical burns, airsickness, gas gangrene, human serum jaundice and shock, are discussed. Although some parts of the book have been rewritten, the method of presentation of the subject has remained unchanged. The reviewer recommends a consultation of this book whenever one wishes needed information on therapy. The book should continue to be one of the important books to be found in the library of any student or practicing physician.

Endocrinology of Woman. By E. C. Hamblen, M.D. Price, $8. Pp. 571, with 157 illustrations. Springfield, Ill.: Charles. C Thomas, Publisher, 1945.

This book is well written. The presentation is concise; the organization of the material is logical, and the bibliography is adequate and up to date at the time of publication. For a textbook of endocrinology the absence of humbug is notable.

The author has presented his material in five parts. Part 1 is concerned with the history, embryology, anomalies, anatomy, chemistry, physiology and interrelation of the various endocrine glands. This ambitious program is well executed in tabloid-like form with adequate annotations and references to support the text.

Part 2 is concerned with applied endocrine physiology: antenatal growth, sexual differentiation, childhood development, sexual maturation, sexual maturity and sexual regression, including chapters on menstruation, conception and gestation. The more recently acquired physiologic concepts are presented.

Part 3 is concerned with endocrine diagnostic methods. Normal values are given. The clinical significance of abnormalities is discussed.

Part 4 has to do with functional disorders of the endocrine glands. This part includes some of the weaker chapters in the book, probably because the author had to draw so largely outside his own clinical experience in discussing such disorders as those of the pancreas and the thyroid.

Part 5 is concerned with endocrinology applied to gynecologic disease. The author presents his therapeutic regimen for various endocrine disorders, including sterility. He makes no wild claims. He is refreshingly frank about the inadequacy of hormonal therapy for painful breasts and dysmenorrhea. On the other hand, there is an annoying tendency on the part of the author to present as fact a favorite hypothesis of his concerning the overactivity of the adrenal in the climacteric. Another failing is the absence of a coherent presentation of the problem of amenorrhea.

This book is recommended to students and practitioners.

Publicaciones del centro de investigaciones tisiológicas. Edited by Prof. Roque A. Izzo, Director. Volume 8. Buenos Aires, Argentina: Pabellon "Las Provincias," Hospital Tornu, 1944.

The eighth volume of research publications from the Hospital Tornu is a faithful continuation of their earlier volumes. This issue contains several valuable contributions on blood chemistry in tuberculosis, with a few academic studies on various normal and pathologic conditions. Some of the latter, together with an exhaustive review of the history of pneumothorax and a reinvestigation of the "leukocytic formulas" in tuberculosis, make the volume useful to those interested in these subjects.

The summaries in four languages of each article are commendable.

Endocrine Man: A Study in the Surgery of Sex. By L. R. Broster, D.M., F.R.C.S. Price, $3.50. Pp. 144. New York: Grune & Stratton, Inc.; London: William Heinemann, Ltd., 1944.

This work represents an attempt to define the role of the neuroendocrine system in a broad prospective by a British surgeon best known to this country for his work on the surgery of the adrenal glands in virilism.

The work is readable. There is no new material presented. However, the presentation of the author's concepts of instincts and of symbiosis is attractive and provocative.

The portion of the book most open to criticism contains the author's presentation of his favorite subject, the adrenogenital syndrome. He sponsors unilateral adrenalectomy for adrenal hyperplasia. He implies consistently excellent results. This hazardous procedure has few if any supporters in this country.

This book will be of more interest to biologists and those with special interests in endocrinology than to practitioners or medical students.

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CONTENTS

PAGE

Effects of Plasma and Fluid on Pulmonary Complications in Burned Patients: Study of the Effects in the Victims of the Cocoanut Grove Fire. Maxwell Finland, M.D.; Charles S. Davidson, M.D., and Stanley M. Levenson, M.D., Boston 477

Hyperactive Cardioinhibitory Carotid Sinus Reflex. M. H. Nathanson, M.D., Los Angeles 491

Systemic Infection Due to Torula Histolytica (Cryptococcus Hominis):

I. Report of Four Cases and Review of the Literature. Glenn Q. Voyles, M.D., and Evart M. Beck, M.D., Indianapolis 504

II. Effect of Chemotherapeutic Agents in Experimentally Produced Infections. Evart M. Beck, M.D., and Glenn Q. Voyles, M.D., Indianapolis 516

Role of Histamine and Acetylcholine in the Mechanism of Heat Allergy: Report of Studies on a Soldier. Captain Gustavus A. Peters and Major Jacob J. Silverman, Medical Corps, Army of the United States 526

Chronic Hemolytic Anemia: Observations on the Effect of Fat Content of the Diet and Multiple Red Cell Transfusions. Robert S. Evans, M.D., San Francisco .. 544

Concentrated Human Albumin in the Treatment of Shock. E. A. Stead Jr., M.D.; E. S. Brannon, M.D.; A. J. Merrill, M.D., and J. V. Warren, M.D., Atlanta, Ga. 564

Progress in Internal Medicine:

Review of Neuropsychiatry for 1945. Stanley Cobb, M.D., Boston 576

Book Reviews 592